Superficial Melanocytic Pathology

Superficial Atypical Melanocytic Proliferations

David E. Elder
Sook Jung Yun

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Diagnostic surgical pathology remains the gold standard for diagnosis of most tumors and many inflammatory conditions in most, if not all, organ systems. The power of the morphologic method is such that, in many instances, a glance at a thin section of tissue stained with two vegetable dyes is sufficient to determine with absolute certainty whether a patient should undergo a major procedure or not, or whether a patient is likely to live a healthy life or die of an inoperable tumor. In such cases, the diagnostic process is one of “gestalt,” a form of almost instantaneous pattern recognition that is similar to the recognition of faces, different brands of automobiles, or breeds of dogs. In other “difficult” cases, the diagnosis is not so obvious. In many of these cases, a diagnosis may be possible, but may be outside of the experience of the routine practitioner. In such a circumstance, it may be possible for a practitioner with more experience—a consultant—to make a diagnosis rather readily. In other cases, the problem may really not be suited to the histologic method. In these cases as well, a consultant may be invaluable in determining that it is simply not possible to make a reliable diagnosis with the materials available. In yet other cases, the diagnosis may be ambiguous, and again a consultant’s opinion can be important in establishing a differential diagnosis that may guide clinical investigation.

There are many fine consultants available to the practicing surgical pathology community. Many of them have authored textbooks, and many of them give presentations at national meetings. However, these materials can offer only a superficial insight into the vast amount of knowledge that is embedded in these individuals’ cerebral cortices—and in their filing cabinets. This series represents an effort to enable the dissemination of this hitherto-inaccessible knowledge to the wider community. Our authors are individuals who have accumulated large collections of difficult cases and are willing to share their material and their knowledge. The cases are based on actual consultations, and the indications for the consultation, when available, are presented, because these are the records of the manner in which these cases presented themselves as being problematic. We have asked the consultants, when possible, to present their consultation letters in much the same form (albeit edited to some degree) as that in which they were first presented, because these represent the true records of the clinical encounter. In addition, we asked the authors to amplify upon these descriptions, with brief reference to the literature, and to richly illustrate the case reports with high-quality digital images. We hope that every reader finds these books to be valuable for reference and for education.

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The common (and most of the uncommon) cutaneous neoplasms derived from skin melanocytes can be divided into two major categories (1). In the first category, there is proliferation of neoplastic melanocytes in the epidermis and similar cells may enter the papillary dermis, without having the capacity to proliferate there. In either case, a mass lesion is not formed in the dermis, and these lesions are termed “nontumorigenic.” In the second category, a mass is formed in the dermis, and the lesions are termed “tumorigenic.” The former category is the subject of this monograph.

Melanocytic neoplasms, like those of other cell types, can be divided into “benign” and “malignant” categories. This seemingly simple division conceals a number of ambiguities. First, the definition of “malignant” is not completely clear. As Foulds pointed out many years ago, malignancy is primarily a clinical concept (2). Even though histopathologic diagnosis is often considered to be the “gold standard” for diagnosis of malignancy, the only proof of malignancy is aggressive behavior leading to death or at least severe adverse functional consequences for the patient. Thus, again according to Foulds, histopathologic diagnosis is merely inferential, serving to predict but not to guarantee or mandate a possible adverse outcome.

A significant problem in cancer diagnosis in general is the existence of “intermediate lesions,” lesions that have some attributes of malignancy, and may progress to malignancy, but, in general, are biologically benign at least after they have been completely excised or otherwise expunged. In the realm of melanocytic pathology, these lesions are often located in the epidermis and superficial dermis, because the epidermis is the normal “home” of melanocytes. Benign melanocytic neoplasms are characterized by histologic attributes of benignancy in general—smaller size, a tendency to symmetry, better circumscription, lack of cytologic atypia and proliferative activity, and so on. Malignant melanocytic neoplasms are characterized by larger size, tendency to asymmetry and to poor circumscription, and by the presence of cytologic atypia and mitotic activity.

Neoplastic proliferations of melanocytes have a number of features in common that help to distinguish them from other tumors, such as a basal cell carcinoma or a sweat gland tumor. They are, of course, comprised of neoplastic melanocytes that (whether benign or malignant) resemble melanocytes in their potential ability to produce melanin pigment, and differ from normal melanocytes in three ways: they tend to retain pigment in their cytoplasm, especially when located in the epidermis and superficial dermis; they tend to lose their dendritic morphology and become either rounded or “epithelioid,” or spindled; and they tend to lose their contact inhibition and form nests often comprised of epithelioid cells, or fascicles often of spindle cells (3). This tendency to nest formation is one of the key features in identifying a lesion as melanocytic especially when pigment is minimal or absent.

Another property common to benign and to malignant lesions distinguishes melanocytic tumors
from most epithelial tumors. This is the tendency of both benign and malignant melanocytes to extend from the epidermal compartment into the stromal compartment. In a benign nevus, this phenomenon is often termed “migration” and is the process whereby nevi that are initially “junctional” and confined to the epidermis become “compound” or epidermal and dermal in character, typically in an “accretive” manner where nests of lesional cells are piled up on one another much in the same manner as a brick wall is built (4). In some nevi such as Spitz nevi and perhaps also congenital nevi, the lesional cells appear to have invaded actively from their original location in the epidermis deep into the reticular dermis (5). Thus, the process of “invasion,” defined as extension of lesional cells from the epidermis into the dermis, cannot be regarded as unequivocal evidence of malignancy in a melanocytic tumor, greatly complicating their interpretation. Indeed, there are many benign lesions that have a substantial dermal component, often forming a tumor or a mass that needs to be distinguished from a tumorigenic melanoma.

The key role of histopathology in the analysis of a melanocytic tumor is the recognition, or exclusion, of a malignant melanoma. Attributes useful in this endeavor, as in other tumors, include both architectural and cytologic features. The junctional component of a melanocytic proliferation commonly provides most of the diagnostic clues, such as the presence or absence of pagetoid scatter or continuous basal “lentiginous” proliferation, coupled with cytologic atypia and mitotic activity. A junctional melanocytic proliferation is defined as a proliferation that occurs in the epidermis along the dermal–epidermal junction. Cells that may be present in the superficial dermis are not considered to be junctional, but dermal. A lesion with both junctional and dermal cells is considered to be “compound” and a lesion with only dermal cells is considered to be “dermal.”

Given the propensity of lesional cells to migrate from the epidermis into the dermis, whether they are benign or malignant, there are many melanocytic proliferations that have both junctional and dermal components. The presence of a dermal component, as mentioned above, is not necessarily an indicator of potential for malignant clinical behavior. Another step of tumor progression is usually necessary, namely the ability of the cells in the dermis to not only survive there but also to proliferate and form an inexorably expanding mass lesion, a property called “tumorigenicity.” Tumorigenicity is often accompanied by “mitogenicity,” or the presence of mitotic activity in the dermal component. These two features, tumorigenicity and mitogenicity, define the “vertical growth phase” (VGP), without which competence for metastasis is not usually present in a melanocytic neoplasm. Some benign lesions such as dermal nevi may be tumorigenic but are usually not mitogenic, and lack severe cytologic atypia and other attributes of malignancy (6,7).

The tumorigenic melanocytic proliferations were discussed in a previous volume of this series (Volume 1). In this present volume, we discuss the nontumorigenic atypical melanocytic proliferations or “superficial atypical melanocytic proliferations” (SAMP). As mentioned above, these are examples of intermediate lesions of tumor progression. Some of these lesions are considered to represent superficial melanomas, even though their prognosis in terms of metastasis is very good indeed. It might then be argued that these lesions should not be considered to be fully malignant. However, experience with anecdotal cases suggests that these lesions (or at least some of them) have if not competence for metastasis, at least competence for local persistence, recurrence, and potential future progression to a fully metastatic neoplasm. These lesions have been characterized as “nontumorigenic” melanomas, and also known as
“radial growth phase” melanomas, because growth in these lesions occurs as it were along the radii of an imperfect circle in the skin. Therefore, the term radial growth phase is a clinical term and perhaps the term “horizontal growth phase” might have more meaning for pathologists. Tumorigenic melanoma represents VGP, a stage of progression in which a tumor mass is formed and the lesion tends to acquire a vertical dimension of growth either out from the skin or into the skin. At this stage, the lesion may have competence for metastasis, depending on other properties such as angioinvasion, lymphatic invasion, and the ability to establish a metastasis at a distant site.

It is of interest that the intermediate melanocytic lesions form a group of cases, some of which are considered to represent malignancies but nevertheless have a very good prognosis as far as the possibility of a lethal outcome is concerned. As already mentioned, many of these lesions have the potential for inexorable progression if not completely removed. Therefore, it could be argued that these lesions are better considered to represent potential but not established malignancies, for which a term such as “severe melanocytic dysplasia” might be appropriate. There is no doubt that lesions of this sort contribute to the problem of “overdiagnosis” of melanoma as in other cancers (8). This concept refers to the inclusion of lesions into the category of malignancy that would not have had the potential to progress to a more significant lesion even if they were not excised. Many of these lesions will fall into the category of “superficial atypical melanocytic proliferations” that are the subject of this book.

Although analysis of features like those described above leads to a correct diagnosis in the vast majority of cases, there are cases that present problems, because of criteria that are conflicting, or otherwise insufficient for a confident determination to be made. These cases are rare (a few per year) in a diversified pathology practice, infrequent (several per month) in a busy dermatopathology practice, and common (several cases per week) in a busy national or international consultation practice. Consultants may therefore build up extensive experience that in most referred cases enable them to make a rapid and correct diagnosis. There is still a residual group of cases, however, in which the difficulties of diagnosis are so considerable that only a descriptive diagnosis can be given, such as “superficial atypical melanocytic proliferation of uncertain significance” (SAMPUS), or “melanocytic tumor of uncertain malignant potential” (MELTUMP) (1). These cases, in general, are the subject matter of this book. It is possible that, in the relatively near future, molecular or other tests currently in development will be more widely available to assist with this interpretation, likely only as an adjunct to traditional diagnosis, and likely only in this small group of “histologically ambiguous” cases (9,10). However, it is also likely that a hopefully much smaller residual group of lesions with unpredictable behavior will continue to exist.

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Sook Jung Yun, MD, PhD

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Acknowledgments

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Although the cases presented in this volume are based on real consultations, potential identifying details such as the age and in some cases the gender of the patients and the sites of the lesions have been changed in order to preserve anonymity.
Melanocytic proliferations can be divided into two major categories, namely tumorigenic and nontumorigenic melanocytic proliferations (1). Tumorigenic proliferations are those in which lesional cells have the capacity for survival in the dermis to form a mass lesion. These lesions may have potential competence for the formation of metastases, which are also tumorigenic proliferations of melanocytes that have spread from the primary site to a distant site. Tumorigenic melanocytic proliferations have been covered in a previous edition of this series under the same name (2).

The nontumorigenic melanocytic proliferations represent proliferations of melanocytes that occur mostly in the epidermis. While they may involve the dermis, a tumor in the true sense (i.e., a mass lesion) is not formed. Most of these lesions are neoplasms, but some may represent a reactive hyperplasia or a hamartoma. The epidermis is the normal “home” of the major population of melanocytes, which are dendritic cells that reside as single cells among basal keratinocytes within the epidermis, forming pigment that for the most part is promptly transferred to the neighboring basal keratinocytes. Neoplastic or other stimuli may result in proliferation of these melanocytes, so that rather than being isolated as single cells among keratinocytes, they lose their dendrites, often retain pigment in their cytoplasm, and become confluent either in the form of nests or as continuous rows of cells.

These neoplastic proliferations may be benign or malignant. Benign melanocytic lesions, like the malignant ones, result from proliferation of melanocytes; however, the proliferation is limited in terms of its scope and duration. Most benign melanocytic lesions, though not all, are small lesions, which result from a relatively brief and limited period of cell proliferation, followed by cessation of that proliferation and a period of stability. Following that period of stability, many of these lesions will actually regress and disappear over time.

Malignant melanocytic proliferations may occur in the dermis or the epidermis, but most of them begin as a proliferation of epidermal melanocytes. In a malignant lesion, the duration of the proliferation tends to be unlimited, resulting in lesions that tend to become increasingly large. As the size of the lesion increases, so do the number of cells and so does the risk that events of “tumor progression” will occur. These events may result in a lesion that acquires additional attributes of the malignant phenotype, such as the properties of tumorigenicity and mitogenicity, the latter representing the ability of the cells not only to survive but also to divide within the dermis, which may then result in tumor formation. Concomitantly, the tumor may over time progressively acquire other attributes of competence for metastasis. Metastasis is the process that usually leads to the death of patients with malignant melanocytic tumors (melanomas). It is very uncommon for metastasis to occur in a patient with a melanoma limited to the nontumorigenic phase of tumor progression, which has been termed the “radial growth phase” (RGP), because it represents
a phase of progression in which melanomas expand, as it were, along the radii of an imperfect circle in the skin as viewed clinically (3).

In the concept of the term “superficial atypical melanocytic proliferations (SAMP),” at least some of the lesions in question may be thought biologically to have the capacity for inexorable proliferation and for subsequent progression to a more advanced lesion; however, at the time of their excision and examination histologically, they lack tumorigenicity and, with almost vanishingly rare exceptions, lack competence for metastasis. Nevertheless it is necessary to distinguish the malignant proliferations from the benign ones because of their propensity for persistence, recurrence at the local site, and progression to a more significant lesion over time. These lesions can be cured by simple excision, emphasizing the importance of recognizing those cases that have this propensity. At the same time, it is important to recognize those lesions that are wholly benign and for which complete excision is unnecessary, in order to avoid overdiagnosis of melanoma, and overtreatment of the patients.

**CLASSIFICATION OF MELANOMA**

Although all melanomas share the commonality that they are malignant tumors derived from melanocytes, there is substantial variation among melanomas in terms of their epidemiology and etiology, clinical and histologic morphology, and genomic underpinnings. The present WHO classification of melanomas is based on literature going back more than 50 years, including seminal studies from McGovern in Australia (4), as well as Clark in the United States (5). These authors recognized clinicopathologic variants of melanoma, allowing for subsequent studies to recognize correlating epidemiologic and genomic variants. The WHO classification is as follows in Table 1.

**TABLE 1 WHO Classification of Melanocytic Tumors**

<table>
<thead>
<tr>
<th>Malignant melanoma</th>
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<tbody>
<tr>
<td>Superficial spreading melanoma</td>
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<tr>
<td>Nodular melanoma</td>
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<tr>
<td>Lentigo maligna</td>
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<tr>
<td>Acral-lentiginous melanoma</td>
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<tr>
<td>Desmoplastic melanoma</td>
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<tr>
<td>Melanoma arising from blue nevus</td>
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<td>Melanoma arising in a giant congenital nevus</td>
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<td>Melanoma of childhood</td>
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<td>Nevoid melanoma</td>
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<tr>
<td>Persistent melanoma</td>
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<td>Benign melanocytic tumors</td>
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<tr>
<td>Congenital melanocytic nevi, Superficial type</td>
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<tr>
<td>Proliferative nodules in congenital melanocytic nevi</td>
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<tr>
<td>Dermal melanocytic lesions</td>
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<tr>
<td>Mongolian spot</td>
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<tr>
<td>Nevus of Ito and Ota</td>
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<tr>
<td>Blue nevus</td>
</tr>
<tr>
<td>Cellular blue nevus</td>
</tr>
<tr>
<td>Combined nevus</td>
</tr>
<tr>
<td>Melanotic macules, simple lentigo, and lentiginous nevus</td>
</tr>
<tr>
<td>Dysplastic nevus</td>
</tr>
<tr>
<td>Site-specific nevi</td>
</tr>
<tr>
<td>Acral</td>
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<tr>
<td>Genital</td>
</tr>
<tr>
<td>Meyerson nevus</td>
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<tr>
<td>Persistent (recurrent) melanocytic nevus</td>
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<tr>
<td>Spitz nevus</td>
</tr>
<tr>
<td>Pigmented spindle cell nevus (Reed)</td>
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<tr>
<td>Halo nevus</td>
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In practice, the classification scheme primarily uses histopathologic characteristics to categorize primary tumors. Clinical morphology is the gross pathology of skin disease, and also correlates with the histopathologic classification, so that the classification scheme is best regarded as clinicopathologic in nature. The clinicopathologic subtypes also correlate
with epidemiologic and genomic aspects of the various subtypes of melanoma. The genomic aspects of importance include primarily presence of activated oncogenes, and the loss of suppressor genes. In any given case, the particular activated oncogenes, and their mode of activation, are of critical importance for targeted therapy of metastatic disease. For primary tumors, the standard therapeutic approach remains surgical, and genomic details are at this time of less importance. Thus, genomic testing is not currently being routinely done until metastasis occurs, and then the genomic information becomes paramount in the selection of therapy. If adjuvant targeted therapy becomes standard for, say, high-risk primary tumors, this situation will change. General aspects of the individual subtypes are discussed in later sections.

**ETIOLOGY/SITE/GENOMIC CLASSIFICATION OF MELANOMA AND ATYPICAL MELANOCYTIC PROLIFERATIONS**

Bastian has recently proposed a classification of the common cutaneous melanomas (SSM, LMM, and AM) based on the presence and degree of chronic solar damage, as measured by the degree of solar elastosis (chronic solar damage [CSD]) (6). In general, this classification also corresponds to the site of occurrence of the lesions on the skin surfaces, and to epidemiologic observations that have related melanoma risk patterns to either acute intermittent sun exposure (e.g., sunburns acquired on weekends), or chronic continuous sun exposure (e.g., that experienced by outdoor workers). Other melanomas appear not to be associated with sun exposure, and solar elastosis is not seen in their resection specimens. For example, acral skin is not susceptible to sunburn because of the protective light-scattering effect of the thick stratum corneum. Mucosal melanomas, including those of the vulva, oral and sinonasal mucosae, are also not associated with sunlight exposure. The scalp may be a sun-protected site in young people and a site of CSD in older men. It is becoming apparent that the genetic basis of melanomas varies according to these patterns, as will be discussed below in the various categories.

The major categories of cutaneous superficial atypical melanocytic proliferations (AMP) classified on the basis of etiology and/or site of origin in the skin are as follows below in Table 2. Because the

<table>
<thead>
<tr>
<th>Classification based on etiology and/or site</th>
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<tbody>
<tr>
<td>1. “Low CSD” superficial atypical melanocytic proliferations (SAMP)</td>
</tr>
<tr>
<td>1.1. Superficial spreading (pagetoid) melanoma</td>
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<tr>
<td>1.2. Dysplastic nevi, lentiginous junctional, and compound nevi</td>
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importance of superficial proliferations, in general, is to distinguish them from melanoma and avoid overdiagnosis, the pathology of the superficial categories of melanomas will be presented first, followed by the descriptions of the major simulants of melanoma. Because not all lesions can be placed into a single diagnostic category, discussion of the descriptive diagnostic concepts of “superficial atypical melanocytic proliferations of uncertain significance (SAMPUS)” and “melanocytic tumor of uncertain malignant potential (MELTUMP),” including approaches to management, will occur throughout the work.

**SUPERFICIAL AND DEEP MELANOCYTIC PROLIFERATIONS—RADIAL AND VERTICAL GROWTH PHASE**

Because this volume is focused on superficial atypical melanocytic proliferations, namely superficial melanomas and their simulants, some discussion of the differences between superficial nontumorigenic versus tumorigenic melanocytic proliferations is appropriate. As briefly discussed above, melanomas can be divided into two major categories: tumorigenic and nontumorigenic, corresponding to vertical growth phase (VGP) and RGP melanomas, respectively.

Most cutaneous melanomas are thought to originate in the epidermis as a junctional proliferation of atypical melanocytes. These may arise in association with a preexisting nevus, or with a lentigo, or in apparently normal skin. These neoplastic melanocytes are characterized by a loss of contact inhibition and a tendency to retain pigment so that histologically one sees melanocytes in contiguity with one another, usually with increased pigmentation compared to normal melanocytes. The latter are cells that lie along the dermal–epidermal junction as single cells, separated by keratinocytes. In Caucasian skin, melanocytes typically do not contain pigment, having transferred it to neighboring keratinocytes after synthesis.

In an evolving RGP melanoma, from an initial focus, the proliferation increases in size, histologically in a linear dimension along the junction. These melanocytes may be present as single cells that tend to form continuous regions of basal proliferation of contiguous melanocytes, or be present as nests of cells along the junction. Clinically, a patch or plaque lesion is formed, which expands along the radii of an imperfect circle in the skin. The term “radial growth phase” therefore refers to the radial dimension of a clinical lesion. In the RGP, the lesional cells may be confined to the epidermis, in which case the lesion is termed “melanoma in situ,” or there may be extension into the dermis of single cells or small nests. The melanoma is then invasive. There is evidence that proliferation of cells in RGP melanomas is limited to the junctional component. If cells are present in the dermis they lack proliferation markers, and if nests are present they remain similar in size or smaller than the largest nests in the epidermis, where they were formed. These cells in the dermis may have capacity for indefinite survival or they may either undergo apoptosis or senescence, or may succumb to an immune response, in the latter case resulting in their disappearance and often resulting in fibroplasia, perhaps caused by cytokine release. In cases where lesional cells in the epidermis and in the dermis are absent in an area of fibroplasia, it is considered likely that preexisting melanoma in this region of a lesion, or sometimes in an entire lesion, has undergone regression. Regression is usually a property of the RGP; however, similar changes may also be seen in VGP nodules, albeit less frequently.

In those cases where the cells in the dermis have capacity for indefinite survival, they may persist as single cells or small nests. However, over time,
there is increasing risk that additional genetic events may occur resulting in the acquisition of competence for not only survival but also proliferation in the dermis. In these cases, there may be expression of proliferation markers including mitotic figures, and clusters of cells may form in the dermis that are larger than the largest clusters or nests in the epidermis. These clusters represent the earliest recognizable stages of VGP. Over time, a small VGP cluster may increase in size to form a tumorigenic papule or nodule. In order for this to occur, the cells in the dermis must have the capacity not only to survive but also to proliferate. Therefore, proliferation, which may be recognized as the presence of mitotic figures in lesional cells in the dermis, is the sine qua non of VGP. In general, with rare exceptions, only tumorigenic melanomas have capacity for metastasis (7,8). VGP is not synonymous with invasion, but depends on the presence of tumorigenicity and/or mitogenicity. A bulky VGP is obvious; however, in an early lesion, minimal VGP has been defined as follows (9): (a) There is a cluster of cells in the dermis that is larger than the largest cluster of cells in the epidermis (tumorigenicity) and/or (b) at least one mitotic figure is present in the dermis (mitogenicity).

In turn, RGP may be defined as a melanoma or a region of a melanoma in which VGP is absent. RGP may therefore exist as “pure” RGP in which VGP is absent from the entire lesion, or as a component of a complex lesion adjacent to a VGP papule or nodule. In the latter case there may be competence for metastasis based on the presence of the VGP; in the former case, the vast majority of these lesions are not associated with metastasis. Rare exceptions that we have observed have usually had relatively extensive areas of regression, suggesting that perhaps a small VGP had been present and had metastasized before it regressed.

**PRINCIPLES OF MANAGEMENT OF SUPERFICIAL ATYPICAL MELANOCYTIC PROLIFERATIONS**

As has been recently reviewed (10), studies have shown considerable disagreement in the histological diagnosis of melanoma, resulting in diagnostic uncertainty and complicating decision making for appropriate treatment (11,12). This occurs because of complexity in the histological continuum from benign to unequivocally malignant melanocytic lesions, and is most pronounced in the gray zone between wholly benign and obviously malignant lesions, which are the subject of this book (13). The difficulties are less problematical within a single institution where patterns of diagnostic terminology and communication have been established. Subjectively, this variation in terminology appears to be especially troublesome between institutions that adhere to different schools of thought. Between institutions, and especially when there is variation in expertise and experience, the level of disagreement can be high (14).

A lack of standardization affects other clinical fields as well as melanocytic pathology. To improve precision in breast imaging, BI-RADS™ (Breast Imaging Reporting and Data System) was developed by a U.S. Food and Drug Administration mandate with the participation of the American College of Radiology. This system standardizes mammogram interpretations on a 5-point scale in an effort to minimize ambiguity regarding the most appropriate therapeutic management. A similar system is under development for the melanocytic tumor system and has been termed the MPATH-Dx (Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis) schema, comprising a Histology Reporting Form and a Diagnosis-Treatment Mapping Tool (10). The terms used in the Histology Reporting Form are still under development and are designed to encompass the whole range of the
“diagnoses” that are used in the field. The impact of variation in the exact form of words used for diagnosis in different classification systems appears to be lessened when management implications are included as a primary outcome of the diagnostic process. The Mapping Tool is essentially a thesaurus that aims to encompass all of the terms in current use and map these to one of five MPATH-Dx categories. These are intended to represent possible clinical approaches to consider for management of a lesion that is assumed for this purpose to be present at a specimen margin. The approaches vary according to the anticipated degree of aggressiveness believed to be associated with each diagnostic category, as follows (10):

**MPATH-Dx Category 0:** Incomplete study due to sampling and/or technical limitations. Clinical Outcome: Repeat testing or short-term follow-up.

**MPATH-Dx Category 1:** Benign lesions with essentially no probability of adverse consequences, for example, common (including mildly dysplastic) nevi, lentigines, and similar disorders. Clinical Outcome: No further treatment required.

**MPATH-Dx Category 2:** Lesions for which the probability of progressive disease is considered unlikely, but some risk for continued local proliferation and possible future adverse consequence cannot be ruled out, for example, some examples of Spitz tumors, deep penetrating nevi, moderately dysplastic nevi. Clinical Outcome: Narrow but complete excision (<5 mm).

**MPATH-Dx Category 3:** Lesions with a higher likelihood of local tumor progression and greater need for intervention, for example, melanoma in situ, most examples of severely dysplastic nevi. Clinical Outcome: Excision with at least 5 mm (but <1 cm) margins.

**MPATH-Dx Category 4:** Lesions with substantial risk for loco-regional progression, for example, invasive melanoma, AJCC Stage T1a. Clinical Outcome: Wide excision (≥1 cm margins).

**MPATH-Dx Category 5:** Lesions with greater risk for loco-regional progression, for example, invasive melanoma, AJCC Stage Tb or more. Clinical Outcome: Wide excision (≥1 cm margins) consider sentinel node staging, possibly other adjuvant therapy.

Substantial health care resources have been directed to the screening of populations considered to be at increased risk of melanoma, as in other neoplastic systems. Ambiguities in diagnostic reports are common, and there is a tendency to electively treat ambiguous lesions. Screening studies have led to an increased number of diagnoses of melanoma, without a concomitant increase in mortality, leading to suggestions that melanoma, like other cancers, is being over-diagnosed at a biological level, even in cases where there is good agreement as to a given diagnosis (15). It follows that there are many cases that never would have progressed to clinical malignancy. Our present criteria do not provide the tools to distinguish harmless lesions from those that would have progressed if not excised, although developing sophistication in genomic studies such as fluorescence in situ hybridization (FISH) has the potential to improve this situation (13). Harm to patients can result not only from undertreatment but also from overtreatment of ambiguous disease in the forms of false fear of cancer, of morbidity from unnecessary treatment, and of misdirection of health care resources (15). These issues result not only from intrinsic limitations of the diagnostic processes but also as a response to medicolegal pressures and patient safety concerns. The MPATH-Dx Diagnostic-Treatment Mapping Tool is preliminary and its recommendations are debatable (16). However, it may serve as an aid in reducing uncertainty and ambiguity in melanocytic lesion reporting and allowing for greater consistency in the management of pigmented lesions, and also by facilitating the study of outcomes and resource allocation at the level of populations and health care systems (10).
References

Superficial Melanocytic Pathology: Superficial Atypical Melanocytic Proliferations
1.0 “Low CSD” Superficial Atypical Melanocytic Proliferations (SAMP)

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1.2 Nevi Including Dysplastic Nevi
   1.2.1 Epitheliod Cell Melanocytic Dysplasia Versus Superficial Spreading Melanoma
   1.2.2 Moderate Versus Severe Dysplasia
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1.3 Recurrent and Traumatized Nevi
   1.3.1 Recurrent Nevus Versus Melanoma
   1.3.2 Recurrent and Traumatized Nevi
   1.3.3 Recurrent Nevus Versus Melanoma
   1.3.4 Recurrent Nevus Versus Melanoma
   1.3.5 Recurrent and Traumatized Nevi
   1.3.6 Nevus Versus Melanoma
As discussed in the Introduction, melanomas can be classified in terms of their etiology and their genetic attributes as well as their morphology. The morphological classification is most relevant in a publication such as this, which considers differential diagnosis of benign and malignant superficial atypical melanocytic proliferations. From a therapeutic point of view, when the lesion is metastatic, the genetic classification is most important as this forms the basis of targeted therapy. From the viewpoint of epidemiology, the etiologic considerations are important, for example, in designing strategies for prevention of melanoma.

The category of “low CSD” superficial atypical melanocytic proliferations includes superficial spreading or “pagetoid” melanoma, and dysplastic nevi. The differential diagnosis of each of these conditions includes primarily the other one. In addition, of course, other forms of melanoma enter the differential, and in particular there is a subset of lentigo maligna melanoma that can resemble dysplastic nevi, known as “nevoid lentigo maligna” or “dysplastic nevus like lentigo maligna.” These are “high CSD” lesions and are discussed in subsequent sections.

Another category of “low CSD” atypical melanocytic proliferation is that of so-called “recurrent” or “persistent” nevi. These are atypical junctional proliferations that appear at the site of a prior shave biopsy of a nevus, and likely represent reactive hyperplasia in response to growth factors in a healing wound. Although not strictly speaking neoplastic, these are atypical proliferations that also tend to occur in low CSD skin, and the differential diagnosis includes dysplastic nevi and melanoma in situ.

In the next three sections, we will discuss these conditions primarily from a morphological point of view. Because it is most important to recognize and specifically diagnose melanomas so that they can be managed appropriately, these are discussed first followed by discussion of their atypical simulants.
Superficial spreading melanoma (SSM) is the most common subtype of melanoma and thus represents the so-called “prototypic melanoma.” This form of melanoma is associated with “acute-intermittent” sun exposure, the type of exposure that is experienced by indoor workers on weekends and vacations. As the prototypic form of melanoma, superficial spreading melanoma is the most familiar to pathologists. Pagetoid scatter of melanocytes into the epidermis is a major distinguishing feature, and was used in the seminal papers of McGovern in Australia to define the term “pagetoid melanoma” (1). At about the same time, Clark had defined the term “superficial spreading melanoma,” which remains in current use (2). The term pagetoid melanoma, however, better describes the histopathologic morphology.

**CLINICAL FEATURES**

Clinically, superficial spreading melanomas like other melanomas with radial growth phase are characterized by the ABCD criteria, originally proposed by Friedman et al. from NYU (3). According to these criteria, “Asymmetry,” where one half of the lesion differs from the other in terms of shape, color, or texture, “Border irregularity,” where lesion may look like the map of a small island with an indented coastline, “Color variegation” with shades of tan, brown, and other colors including “red white and blue,” and increased “Diameter” are reasons for concern in a pigmented lesion. These criteria are, of course, not perfectly sensitive or specific. It has been suggested to add “E” to reflect “Elevation”; however, not all melanomas are elevated or palpable at their inception. “Evolution” or history of change is also an important criterion for distinguishing melanomas from benign nevi. Changing lesions in general should be excised for diagnosis irrespective of their morphology unless a confident clinical diagnosis of the benign entity can be made. As they evolve, melanomas begin to look different from a patient’s background nevi, resulting in the “ugly duckling” sign where a lesion appears to be out of step with other lesions, and such lesions also should be considered for excision (4).

Although other technologies are beginning to become available, the gold standard for diagnosis of a melanoma remains histologic examination of a clinically selected lesion. Histologic evaluation of clinically unselected lesions, not the typical practice, would be expected to have lesser degrees of specificity, so that accurate diagnosis depends on both clinical as well as histologic morphology. As is true of skin pathology in general, the clinical morphology is the gross morphology of the condition, and clinical photography, as well as gross photography of the specimen in the laboratory, may be of considerable assistance in making an accurate diagnosis where histologic criteria are ambiguous.

**ETIOLOGY/SITE/GENOMIC CLASSIFICATION FOR SSM**

Superficial spreading melanomas tend to occur on skin that is intermittently exposed to the sun and
has been called the “no CSD” category of melanoma, which tends to be associated with BRAF mutations, in younger age (5,6). However, in our practice we usually identify some degree of solar damage usually in the mild to moderate range in reexcision specimens for superficial spreading melanomas. Therefore we would prefer to categorize superficial spreading melanoma as in a “low CSD” category, and only rarely in a “no CSD” category. Superficial spreading melanoma is the most common form of melanoma in Caucasian populations (7). This form of melanoma is also the one most commonly associated with mutations of the BRAF oncogene (8). Epidemiologically, this form of melanoma is most highly associated with nevi and especially dysplastic nevi as risk factors (9). Lentigines, although more strongly associated with high CSD melanomas, are also independent risk factors for development of superficial spreading melanoma.

**HISTOPATHOLOGY**

The histologic criteria for diagnosis of superficial spreading melanoma and distinguishing it from other subtypes were described in seminal papers by McGovern (1) and Clark et al. (2). In a recent study, a series of melanomas were classified by WHO type, and also by mutation status (5,10). The lesions were classified as SSM, LMM, ALM, and NM, and a not classified group. The histologic attributes studied were graded into low, medium, and high values. The superficial spreading melanoma subtype (compared to the lentigo maligna subtype) was associated with high pigment, high scatter, high nesting, good circumscription, a thickened epidermal contour, and larger cell size. The degree of solar elastosis was lower. These findings are similar to those in earlier studies, except that pigmentation had not previously been emphasized as a distinguishing feature from lentigo maligna melanoma. These attributes, in general, were also associated with mutation of the BRAF oncogene.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of superficial spreading melanoma includes the other melanoma subtypes, to be discussed in sections following. This distinction is of some diagnostic and epidemiologic importance but in general does not correlate with biologic behavior or influence management. An exception to this general rule is the finding that superficial spreading melanomas tend to be better circumscribed than lentiginous melanomas, which can mean that specimen margins are easier to evaluate both clinically and histologically. As a result, local persistence of in situ melanoma followed by recurrences is probably less frequent in this subtype. In general, persistence of in situ melanoma, caused by failure to completely excise the primary lesion, will be followed by recurrence of in situ/radial growth phase disease. This disease would likely be cured by a subsequent complete excision. If, however, the disease is allowed to persist, further progression may occur with development of vertical growth phase, increasing thickness and mitotic activity, and potential for development of metastasis.

Melanocytic nevi constitute the other major group of differential diagnostic considerations. Chief among these are dysplastic nevi; however, the pigmented spindle cell nevus of Reed is also a lesion that may present overlapping features as may pagetoid Spitz nevi/tumors. In these latter cases, the lesions tend to be small, circumscribed, and comprised of large spindle and/or epithelioid cells. Kamino bodies may be present (see Section 7).

Dysplastic nevi (Section 1.2) are the most frequent consideration in the differential diagnosis of superficial spreading melanoma. Features that may be of assistance in making this distinction are listed in
Table 1.1. These include architectural and cytologic features relating to both the junctional and dermal components. The most important criteria include smaller size and greater symmetry of the dysplastic nevi compared to superficial spreading melanomas. Pagetoid scatter tends to be lacking or minimal in the nevi, which in contrast have predominance of nests that bridge between adjacent elongated rete ridges. Melanomas tend to be characterized by diffuse fibroplasia in the papillary dermis, at least when they are invasive, compared to the concentric eosinophilic fibroplasia seen in dysplastic nevi. Cytologically, melanomas are characterized by moderate to severe uniform atypia (atypia often involving greater than 50% of lesional cell nuclei), while dysplastic nevi are characterized by mild to moderate atypia involving usually less than 5% of the lesional cells. These percentages are not absolute and cases with intermediate values of these and other criteria can be considered in isolation. Mitotic activity is a very important distinguishing feature, particularly when mitoses are present in the dermis. Junctional mitoses are of lesser significance; however, as a rule of thumb, we generally consider that a lesion presenting a dichotomous differential diagnosis between severe dysplasia and melanoma would be more likely to be a melanoma if junctional mitoses are present.

**PRINCIPLES OF MANAGEMENT OF SSM**

Superficial spreading melanoma is managed according to criteria that are nationally promulgated by organizations like NCCN, according to AJCC staging criteria (11,12). Briefly, considering only the superficial melanomas that are the subject of this treatise, melanoma in situ is generally managed by complete local excision with a 5 mm margin. This is MPA T1a lesions (according to the AJCC less than 1.01 mm in Breslow thickness but more typically less than 1.0 mm in common usage) are managed by complete excision, usually with a

<table>
<thead>
<tr>
<th>Feature</th>
<th>Melanoma</th>
<th>Dysplastic Nevus</th>
<th>Nevus</th>
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<tbody>
<tr>
<td>Size</td>
<td>Larger</td>
<td>Intermediate</td>
<td>Smaller</td>
</tr>
<tr>
<td>Symmetry</td>
<td>Poor</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Rete ridges</td>
<td>Irregular</td>
<td>Uniformly elongated</td>
<td>Uniform</td>
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<td>Melanocytes</td>
<td>Epithelioid</td>
<td>Mixed</td>
<td>Nevoid</td>
</tr>
<tr>
<td>Nested</td>
<td>Variable</td>
<td>Predominant</td>
<td>Predominant</td>
</tr>
<tr>
<td>Nests</td>
<td>Coalescent</td>
<td>Bridging</td>
<td>Discrete</td>
</tr>
<tr>
<td>Lentiginous</td>
<td>Continuous</td>
<td>Discontinuous</td>
<td>Discontinuous proliferation</td>
</tr>
<tr>
<td>Pagetoid</td>
<td>High, extensive</td>
<td>Low, focal, minimal</td>
<td>Minimal proliferation</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td>Uniform atypia, random atypia</td>
<td>Minimal moderate-severe</td>
<td>Mild-moderate</td>
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<tr>
<td>Mitoses</td>
<td>About 1/3 of cases</td>
<td>Almost always absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Fibroplasia</td>
<td>Diffuse</td>
<td>Concentric</td>
<td>Minimal</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Bandlike, lichenoid</td>
<td>Patchy, perivascular</td>
<td>Minimal</td>
</tr>
<tr>
<td>Regression</td>
<td>Frequent, extensive</td>
<td>Rare, minimal</td>
<td>Absent</td>
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<tr>
<td>Dermal cells</td>
<td>Uniform atypia</td>
<td>Random or no atypia</td>
<td>No atypia</td>
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<tr>
<td></td>
<td>Limited maturation</td>
<td>Maturation</td>
<td>Maturation</td>
</tr>
<tr>
<td></td>
<td>May be mitoses</td>
<td>No mitoses</td>
<td>No mitoses</td>
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1 cm margin (Category 4). T1b lesions are lesions in the same thickness category but with a stage modifier, either ulceration or “mitogenicity,” the latter term indicating the presence of at least a single mitosis. These are managed by excision, typically with a 1 cm margin and by a consideration of sentinel node staging (Category 5). In current usage, many authorities recommend offering sentinel node staging to people with T1b melanomas only in the upper quartile of thickness in this group, >0.75 mm, in Breslow thickness (11). Interestingly, this is the thickness number that was identified by Breslow as a cutoff between very low risk and “some risk” melanomas in his study of 97 cases published in 1970 (14), and it is also very close to the thickness of 0.78 mm that was identified as a cutoff for “very low risk” in a study of 26,291 thin melanomas from the population (15) based SEER tumor registry.

References
1.1.1

SSM Thin Mitogenic Versus Atypical Nevus With Mitoses

**Clinical Information**
Lesion from the left back of a 50-year-old man.

**Reason for Consultation**
What would you think of this being a very small melanoma? Asymmetry, multiple cell morphologies, and a few mitoses in the dermal component, in a 2 mm lesion.

**Description**
These sections show a melanocytic proliferation which, although small at only 2 to 3 mm in diameter on the slide, is comprised of uniformly atypical large epithelioid melanocytes, present in nests and as single cells near the dermal–epidermal junction, and protruding into the papillary and upper reticular dermis. Lesional cells show little or no evidence of maturation.

**Figure 1.1.1** Scanning magnification shows a relatively small plaquelike lesion.

**Figure 1.1.2 and Figure 1.1.3** The lesion is relatively well circumscribed. Most peripheral cells are nested.
8

SECTION 1.1: SUPERFICIAL SPREADING MELANOMA

1.1.1

FIGURE 1.1.1.4 There is confluence of nests and severe uniform atypia. Pagetoid scatter is not prominent. There is abundant (high grade) pigment.

from superficial to deep. They exhibit moderate but relatively uniform atypia in the form of nuclear enlargement, some hyperchromatism, and prominent nucleoli. In one portion of the lesion, the cells appear to infiltrate among associated, more nevoid cells suggestive of a dermal nevus; however, these cells also exhibit cytologic atypia and after some searching I found a mitotic figure in one of them, so I believe that they are better regarded as differentiated melanoma cells. In the overlying and focally in the adjacent epidermis, there is pagetoid scatter of atypical lesional cells. I believe that this lesion must be interpreted as a melanoma because of the uniform atypia, failure of maturation, the scattered dermal mitoses, and the pagetoid scatter in the epidermis. The lesion is not a Spitz tumor because the lesional cells are not uniform from side to side. One might consider an unusual form of combined nevus; however, the pagetoid scatter and the adjacent intraepidermal component, as well as the mitotic activity, are not features of these lesions. I would therefore interpret this lesion as a melanoma, characterizing it as follows:

FIGURE 1.1.1.5 A mitotic figure is identified in a dermal nest.

DIAGNOSIS

Skin, right shin: Malignant melanoma, superficial spreading type, with “thin” tumorigenic but mitogenic early vertical growth phase, nonulcerated, Clark’s level IV, greatest Breslow thickness 0.56 mm, see Description and Comment.

COMMENT

The dermal mitotic rate in this lesion is 1/mm², tumor-infiltrating lymphocytes are sparse, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is mild
actinic elastosis. The significance of Clark's level IV is likely minimal in this context; however, this lesion is best classified as an AJCC stage Ib primary melanoma because of the presence of dermal mitotic activity. The lesion appears to be relatively narrowly and completely excised. An additional procedure would be indicated, and consideration of sentinel lymph node sampling because the lesion is mitogenic.

**OVERALL COMMENT**

In current practice, sentinel node staging is often not recommended for T1b lesions less than 0.76 mm in Breslow thickness because studies have shown a small yield of positive nodes in these lesions. Therefore this is an MPATH DX Category 4 or 5 lesion.
1.1.2

**Thin Mitogenic Melanoma Versus Nevus With Mitoses**

**Clinical Information**
Lesion of left shin with a mottled color in a 27-year-old woman.

**Reason for Consultation**
I am enclosing for your consultation a melanocytic lesion present for many years from the right shin of a 27-year-old woman. Though the lesion had not changed (according to the patient), her clinician decided to remove it because he “didn’t like the mottled color.”

**Description**
These sections show a superficial atypical melanocytic proliferation that presents considerable difficulties of interpretation. At the periphery, this relatively broad and moderately cellular lesion is comprised mainly of nested large epithelioid melanocytes with abundant cytoplasm that contains finely divided “dusty” melanin pigment. There are some bridging nests between adjacent rete, and these appearances could be consistent with junctional melanocytic dysplasia of the epithelioid type. Toward the center of the lesion, however, there is some variation in size, shape, and orientation of nests with a tendency to confluence of nests, and some similar cells protrude into the upper dermis showing little evidence of maturation and, more importantly, two dermal lesional cell mitoses are present. Given this combination of failure of maturation and mitotic activity, as well as a slight tendency to pagetoid scatter of lesional cells to the midspinous layer in this region, I believe that this lesion is best interpreted as a thin nontumorigenic but mitogenic melanoma, which I would characterize as follows:

*Figure 1.1.2.1* Scanning magnification showing a cellular, asymmetrical lesion.
CASE 2: THIN MITOGENIC MELANOMA VERSUS NEVUS WITH MITOSES

1.1.2

DIAGNOSIS

Skin, left back: Malignant melanoma, superficial spreading type, with nontumorigenic and mitogenic vertical growth phase, Clark's level II, greatest Breslow thickness 0.51 mm, see Description and Comment.

FIGURE 1.1.2.2 Right side of lesion.

FIGURE 1.1.2.3 Right side of lesion showing predominantly basal proliferation of uniformly large epithelioid melanocytes.

FIGURE 1.1.2.4 Center of lesion showing large nests tending to confluence.

FIGURE 1.1.2.5 Dermal mitotic activity in atypical cells that resemble those in epidermis. This mitosis could be considered junctional; however, there seems to be a wisp of collagen between the nest, which is predominantly located in the dermis, and the overlying junctional nest.
1.1.2

**COMMENT**

The differential diagnosis for this lesion could include severe dermal and epidermal melanocytic dysplasia; however, dermal (or even epidermal) mitotic activity essentially rules out this diagnosis. The lesion is not, of course, a Spitz nevus/tumor. The dermal mitotic rate by definition in this lesion is 2/mm², tumor-infiltrating lymphocytes are essentially absent in relation to the invasive component, with brisk noninfiltrating lymphocytes nearby, there is focal radial growth phase regression characterized by diffuse fibroplasia of the upper dermis with absence of lesional cells in the overlying epidermis or in the dermis in the region, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is evidence of an associated junctional dysplastic nevus of the epithelioid subtype, and actinic elastosis in the adjacent dermis is present and mild. This lesion appears to be completely excised with a closest border of approximately 1 mm.

**OVERALL COMMENT**

According to an official clarification of the original AJCC staging manuscript, mitoses should be counted in a “hot spot,” counting adjacent fields until a whole square millimeter has been evaluated and the number of mitoses should then be reported as a whole number (16). There should be no correction for lesions where the area of dermal tumor is greater than 1 mm². If the amount of dermal tumor is less than 1 mm², as in this case, the number of mitoses should be counted and presented again as a whole number without correction for unit area. The mitotic rate for this lesion should be designated as a whole number, namely “1.” The designation of a mitotic rate as “<1” is confusing because it has been used when no mitoses are seen and is interpreted by tumor registrars as synonymous with “zero.” “Thin” mitogenic melanomas represent AJCC Stage Ib melanomas for which sentinel node sampling can be considered. Many authorities currently will limit this procedure to those lesions in the upper ranges of thickness within this category (e.g., >0.75 mm) (17). Therefore this is an MPATH DX Category 4 or 5 lesion.
1.1.3
SSM With Extensive Regression Versus Regressing Nevus
(Halo Nevus)

**CLINICAL INFORMATION**
M41, R Shoulder, shave. r/o melanoma.

**REASON FOR CONSULTATION**
We would appreciate your opinion on this case. The clinical impression is rule out melanoma.

**DESCRIPTION**
These sections show a broad, superficial shave biopsy of skin, containing an asymmetric and focally highly cellular proliferation of uniformly atypical relatively large epithelioid melanocytes arranged predominantly in nests, with some bridging nests but also with areas of confluence of nests. In addition, focally a few of these atypical cells extend up into the epidermis in a pagetoid pattern, though generally not beyond the lower third. In the dermis in this area, there is a brisk band-like lymphocytic infiltrate and at least one cluster of uniformly atypical cells is present in the dermis without evidence of maturation. Together these features present

![FIGURE 1.1.3.1](image1) Scanning magnification shows a broad, plaquelike lesion with irregular distribution of cells in the superficial dermis.

![FIGURE 1.1.3.2](image2) There is a dense bandlike lymphocytic infiltrate at one periphery of the lesion.

![FIGURE 1.1.3.3](image3) Pigmented melanophages are admixed with lymphocytes.
Elsewhere, there is diffuse fibroplasia with scattered lymphocytes and melanophages, consistent with regression.

In another profile, there is again asymmetric distribution of cellularity in the superficial dermis.

There are clusters of cells in the dermis that vary in size and shape. Those of the base show nevoid maturation and may represent a preexisting nevus.

A more superficial cluster demonstrates severe uniform cytologic atypia, most consistent with a remnant of invasive melanoma in a largely regressed lesion.

Taking all of these features together, in my opinion the nested proliferation is best interpreted as melanoma, perhaps arising in a dysplastic nevus with a “congenital pattern” dermal component, with a focus of superficial invasion, which I would characterize as follows:

somewhat borderline features of superficially invasive nontumorigenic and nonmitogenic melanoma, overlapping with severe dermal and epidermal dysplasia. In continuity with this process, however, is a region of extensive regression characterized by widening of the papillary dermis with fibroplasia and melanophages, with a few residual atypical cells present in a continuous basal proliferation in the epidermis, diagnostic of residual melanoma in situ in an area of regression.
At the left periphery of the field seen in Figure 2.1.3.5, there are nests in the epidermis and nevoid cells in the dermis consistent with a compound nevus with congenital and dysplastic features.

**DIAGNOSIS**

Skin, right shoulder: Malignant melanoma, superficial spreading type, with focally invasive nontumorigenic and nonmitogenic radial growth phase, Clark’s level II, greatest Breslow thickness 0.18 mm, and with extensive regression, see Description and Comment.

**COMMENT**

The dermal mitotic rate is zero in the invasive melanoma component, tumor-infiltrating lymphocytes are brisk, there is extensive radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion in this material. There is evidence of an associated compound dysplastic nevus. Actinic elastosis is mild to moderate. Changes extend to base and margins of the shave biopsy specimen.

**OVERALL COMMENT**

Extensive regression has been considered as a possible marker of thin melanomas at greater than average risk (based on the possibility of “down-staging” by the regression, and also by results from some prognostic studies); however, this has not proven to be a strong predictor of lymph node involvement, and current practice would not usually involve recommendations for sentinel node staging in a lesion with these features. This is an MPATH DX Category 4 lesion.
1.1.4

Thin SSM Versus Pagetoid Spitz Tumor in a Child

CLINICAL INFORMATION
Lesion of left neck in a 12-year-old boy.

REASON FOR CONSULTATION
We would value your opinion of this biopsy from the right neck of a 12-year-old boy. Slides have been reviewed by multiple pathologists. There is some divergence of opinion as to how best to report the lesion as MELTUMP or malignant melanoma, with the general feeling that it should be reported as if it were melanoma. Given the young age of the patient and our inability to explain the atypia in terms of an alternative diagnosis (e.g., Spitz nevus or special site nevus), we would be grateful for your review and any advice regarding management of the lesion.

DESCRIPTION
These sections show a moderately to highly cellular proliferation of large epithelioid melanocytes, present in the epidermis as single cells and nests, with quite extensive pagetoid scatter of single cells and nests into the epidermis extending to the stratum corneum. Occasional lesional cell mitosis is present in the junctional component. Similar cells protrude into the papillary dermis in some of the section planes submitted for review, constituting early invasive nontumorigenic and nonmitogenic radial growth phase melanoma. I do not believe this lesion is a Spitz nevus/tumor because the cytology is that of epithelioid rather than epithelioid and/or spindle cells, and there is variation in cytology from side to side. In addition, characteristic architectural features including Kamino bodies are lacking. I would therefore interpret this lesion as follows:

FIGURE 1.1.4.1 Scanning magnification shows an asymmetrical proliferation with a junctional component to the left of the follicular unit and a more densely cellular proliferation to the right.
**FIGURE 1.1.4.2** There is an increased number of moderately atypical nevoid to epithelioid melanocytes in the epidermis, with areas of continuous basal proliferation and pagetoid scatter, and extension down a follicular appendage.

**FIGURE 1.1.4.3** In the center of the lesion, there is a highly cellular proliferation of uniformly atypical epithelioid melanocytes, and a bandlike lymphocytic infiltrate in the dermis.

**FIGURE 1.1.4.4** There is extensive pagetoid scatter into the epidermis.

**FIGURE 1.1.4.5** Cells similar to those in the epidermis are present in the papillary dermis with little or no evidence of maturation.
As noted above, I do not believe this lesion can be classified as a Spitz tumor or special site nevus. Despite this diagnosis, importantly, the dermal mitotic rate is zero, tumor-infiltrating lymphocytes are brisk, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is evidence of an associated dermal nevus. There is no significant actinic elastosis. Changes extend within less than 1 mm of lateral this border. Based on this diagnosis I would, of course, recommend assessment of this young patient’s other melanoma risk factors and perhaps assessment of his family as well, especially if she should have other clinically atypical pigmented lesions and/or a family or personal history of melanoma. An additional excision procedure should, of course, be done, and I would expect the prognosis for cure of this lesion to be excellent.

Although this is a young patient, the incidence of melanoma of the usual “adult” sort begins to increase in the teen and late preteen years. The possibility of a genetic basis could be considered; however, this finding alone is not strongly predictive of a mutation in CDKN2A (which encodes the p16 tumor suppressor and is the strongest melanoma-associated gene), unless there is also a strong family history (18). This is an MPATH DX Category 4 lesion.
1.1.5

SSM Versus LMM Versus Atypical Nevus

**CLINICAL INFORMATION**
Recently developed lesion of the left scapula in a 49-year-old man.

**REASON FOR CONSULTATION**
This is reported to have appeared within the last 4 to 6 months. With the recent onset I believe it to be a melanoma. Do you think there is a preexisting nevus?

**DESCRIPTION**
These sections show a punch biopsy of skin, containing a moderately to rather highly cellular proliferation of uniformly atypical large epithelioid melanocytes. The lesion is poorly circumscribed at one periphery, with the last cell being a single cell rather than a nest, and is transected at the other specimen margin. There is moderately extensive pagetoid scatter of lesional cells into the epidermis, and to the stratum corneum. There is also moderate nesting with a tendency to confluence of nests and variability in their size, shape, and distribution. Similar clusters of cells protrude into the papillary dermis, and into the upper reticular dermis. There is no clear evidence of tumorigenic proliferation or mitotic activity in the dermis; however, the lesional cells show only slight evidence of maturation from superficial to deep with some cells at the base having quite large, irregular, and hyperchromatic nuclei. Although one might consider the possibility of a pigmented spindle cell nevus, this lesion is not symmetrical, the cells are not uniform large spindle and/or epithelioid or narrowly elongated spindle cells, and the lack of maturation of the dermal component is an additional concerning feature. For these reasons I would agree with your interpretation of this lesion as a melanoma, which I would characterize as follows:

**Figure 1.1.5.1** A broad, highly cellular plaquelike lesion within irregular distribution of cells.
1.1.5

**Figure 1.1.5.2** Toward the center the lesion, there is a dermal component composed of clusters of cells of similar size, pile up on top of one another to form a tumorlike proliferation but without expansile growth.

**Figure 1.1.5.3** The nests are built up like a brick wall with one nest piled on top of another. This is termed an “accretive” pattern of vertical growth phase.

**Figure 1.1.5.4** The cells in the accretive vertical growth phase demonstrate moderate uniform cytologic atypia. There is no mitotic activity. This pattern of growth is nonmitogenic and nontumorigenic.

**Figure 1.1.5.5** At the periphery of the lesion there is a junctional component, which has overlapping features between melanoma in situ and severe melanocytic dysplasia. There is moderate (i.e., significant) actinic elastosis.
COMMENT

The dermal mitotic rate in this lesion is zero, tumor-infiltrating lymphocytes are focally brisk but overall nonbrisk, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. Changes of in situ melanoma extend to a lateral specimen border. Although there is some evidence of maturation of the dermal component, I believe that there is cytological and architectural continuity between the somewhat more nevoid cells in the dermis and the overlying in situ melanoma component. Actinic elastosis in the dermis is mild to moderate. There is no definitive associated nevus. In situ melanoma extends to a lateral specimen margin. This is an MPATH DX Category 4 lesion.

OVERALL COMMENT

“Accreting” or “variant” vertical growth phase was described by Richard Reed as a pattern in which lesional cells extend into the dermis as small clusters or nests, which then pile up on one another as a brick wall is built. A mass lesion is then formed, but without “expansile” growth in the dermis, constituting a nontumorigenic variant vertical growth phase pattern. In most cases, there is no dermal mitotic activity, and the prognosis is good by AJCC and other staging systems.
Severely Dysplastic Nevus Versus Melanoma

CLINICAL INFORMATION
Atypical nevus favored over melanoma in a lesion of the left calf of a 36-year-old man.

REASON FOR CONSULTATION
It is a borderline lesion—I favor a severely atypical compound (predominantly junctional) nevus, although it could also be interpreted as melanoma (Clark's level II, Breslow 0.14 mm). What do you think?

DESCRIPTION
These sections show a shave biopsy containing a moderately to highly cellular lesion that measures only about 3 mm in diameter on the slide, located in skin with moderate actinic elastosis. At one periphery of the lesion, there are small nests comprised of relatively small nevoid to epithelioid cells with a few bridging nests, consistent with moderate to severe melanocytic dysplasia. Toward the center of the lesion, however, the rete ridge pattern is effaced and there is a considerably more cellular proliferation of nests that vary somewhat in size and shape and single cells with focal areas of continuous basal proliferation. I would regard these changes are borderline for melanoma in situ versus severe melanocytic dysplasia. In addition, however, there is diffuse fibroplasia in the papillary dermis and there are several clusters of cells similar to those in the epidermis, present in the papillary dermis.

FIGURE 1.1.6.1 A broad superficial lesion with a somewhat irregular architectural silhouette.
A moderately to highly cellular proliferation of single and nested melanocytes, mainly near the dermal–epidermal junction. At one periphery, the lesion is rather poorly circumscribed.

Nests are irregularly spaced and tend to hang down from the interface. There is a brisk lymphocytic infiltrate in the dermis. There is moderate (i.e., significant) actinic elastosis in the dermis.

There is severe uniform cytologic atypia and there is a cluster of cells in the dermis similar to those in the epidermis, located in a region of diffuse fibroplasia and nearby noninfiltrating lymphocytes.

These cells do not appear to be maturing well along nevic lines and they have, in many cases, prominent nucleoli. I am concerned that these changes likely without tumorigenic proliferation or mitotic activity.

Melan-A staining demonstrates dense confluent proliferation in the epidermis with rather more pagetoid scatter than was apparent in the H & E stain.
represent invasive nontumorigenic and nonmitogenic melanoma, however, I will request Melan-A and Ki-67 stains to support the diagnosis. For the present I will interpret this lesion descriptively as follows:

**PROVISIONAL DIAGNOSIS**
Skin, left calf: Superficial atypical melanocytic proliferation of uncertain significance, most consistent with malignant melanoma, superficial spreading type, nonmitogenic and nontumorigenic invasive radial growth phase only, nonulcerated, Clark’s level II, Breslow thickness 0.56 mm, see Description and Comment.

**COMMENT**

**COMMENT 1**
As noted above I favor interpretation of this lesion as a melanoma; if so interpreted, the dermal mitotic rate is zero, tumor-infiltrating lymphocytes are focally brisk but overall nonbrisk, there is diffuse fibroplasia but no fully developed radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. The differential diagnosis could include severe melanocytic dysplasia. Special stains as noted above are pending.

**COMMENT 2 (A FEW DAYS LATER)**
Ki-67 and Melan-A immunostains have been reviewed. The latter shows moderately extensive pagetoid scatter in the epidermis, supporting the diagnosis of melanoma in situ. The section stained with Ki-67 does not include the atypical cells in the dermis and is therefore noncontributory in assessing invasion. I would therefore interpret this lesion as a melanoma.

**FINAL DIAGNOSIS**
Skin, left calf: Malignant melanoma, superficial spreading type, nonmitogenic and nontumorigenic invasive radial growth phase only, nonulcerated, Clark’s level II, Breslow thickness 0.56 mm, see Description and Comment.

**OVERALL COMMENT**
Although this lesion has nevoid attributes and morphologically overlaps with a dysplastic nevus, I believe it is best interpreted as melanoma because of its cellularity, severe uniform atypia, and the lack of nevoid maturation. The lesion is borderline and it is possible that fluorescence in situ hybridization (FISH) analysis could contribute to a more specific diagnosis, if desired. In either case, the lesion should be completely excised with an appropriate margin (MPATH DX Category 3 or 4).
1.1.7

SSM In Situ Versus SAMPUS—Severe Dysplasia

CLINICAL INFORMATION
A variegated atypical lesion on the chest of a 46-year-old woman.

REASON FOR CONSULTATION
Melanoma.

DESCRIPTION
These sections show a shave biopsy of skin, containing a moderately to focally, more highly cellular proliferation of moderately large epithelioid melanocytes, arranged singly and in groups along the dermal–epidermal junction. There is a tendency to confluence of the nests, and variation in their size, shape, and distribution, and there is also focal pagetoid extension of single cells into the epidermis, focally as far as the stratum granulosum at least. Deeper sections and immunostains are noncontributory as they include only a small portion of the lesion, if any. The differential diagnosis for this lesion could include a severely dysplastic nevus; however, the presence of fairly frequent mitoses, uniform atypia, and pagetoid scatter in the junctional component would argue against this diagnosis. One might also consider a pigmented spindle cell nevus, but the lesional cells are not the characteristic narrow long elongated heavily pigmented spindle cells of that lesion and there is variation in architecture across the lesion from side to side. I would therefore characterize this lesion as follows:

FIGURE 1.1.7.1 A broad, superficial lesion with an irregular profile.
FIGURE 1.1.7.2 At its left edge, the lesion is poorly circumscribed with the last cells being single cells.

FIGURE 1.1.7.3 At the right edge there is good circumscription, with bridging nests that could represent a pre-existing dysplastic nevus, although cytologically the cells resemble those in the remainder of the lesion.
Skin, left chest: Melanoma in situ, superficial spreading type, completely excised, see Description and Comment.

The lesion appears to be possibly arising in a junctional dysplastic nevus, and there is mild actinic elastosis in the dermis. This lesion is quite well circumscribed and is completely excised with closest borders of approximately 2 mm, to the lateral margins. There is involvement of a skin appendage extending within 0.5 mm of the specimen base.

This is a lesion of sun-exposed skin albeit with mild chronic solar damage. MPATH DX Category 3.
**CLINICAL INFORMATION**

Lesion of right upper arm in a 22-year-old man, atypical nevus versus melanoma.

**REASON FOR CONSULTATION**

This biopsy shows significant junctional and dermal cytologic atypia and we are considering the possibility of early malignant melanoma. This melanocytic neoplasm has very worrisome features such as junctional and dermal cytologic atypia and lack of maturation, but it does not show junctional contiguity of melanocytic proliferation and pagetoid spread, but the possibility of an early melanoma was raised and it was reviewed at the intradepartmental consensus conference. This case will be sent for consultation.

**DESCRIPTION**

These sections show a melanocytic proliferation that is relatively small but moderately to highly cellular and is comprised of a uniform population of large epithelioid cells arranged predominantly in nests, predominantly near the dermal–epidermal junction, with a tendency to confluence of nests from side to side. Similar cells protrude into the papillary dermis where they show little or no evidence of maturation. They are present in nests in the dermis, none of which is larger than the largest intraepidermal nest. The cells have abundant cytoplasm with finely divided melanin pigment, and large, somewhat pleomorphic nuclei with prominent nucleoli. Although not extensive, there is focal slight pagetoid scatter.

**FIGURE 1.1.8.1** A highly cellular plaquelike lesion.
The lesion is comprised of large epithelioid melanocytes. The last cells are in the form of a nest at the periphery.

The nests vary considerably in size, shape, and orientation.

Mitotic activity is present in superficially located dermal nest.

There is little evidence of maturation toward the base of the lesion.

HMB 45 stains cells in the dermis, another indicator of impaired “maturation.”

into the epidermis. The confluence of nests, the uniform cytologic atypia, and the failure of maturation are concerning for melanoma, and this impression is supported by the finding of junctional mitotic activity and at least two dermal mitoses, which happened to be in one high-power field, with one of them being present in cells infiltrating the upper reticular dermis. There is also Ki-67 proliferative activity of junctional and dermal cells. I would therefore agree with your concern and would characterize this lesion as follows:
COMMENT

Despite the youthful age of the patient, this lesion is not a Spitz tumor because it is not comprised of large spindle and/or epithelioid cells, the finely divided melanin pigment is more characteristic of melanoma, there are no Kamino bodies at the interface, there is failure of maturation, and there are dermal mitoses including one in the lower third of the lesion. The dermal mitotic rate by convention is 2/mm², tumor-infiltrating lymphocytes are sparse and focal, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is no associated nevus. Despite the relative youth of the patient, there is evidence of mild actinic elastosis in the adjacent dermis. The lesion is completely excised with closest borders of approximately 1 mm in the section planes available for study. In summary, this is a “thin” AJCC stage Ib lesion, for which an additional definitive excision procedure would be recommended.

OVERALL COMMENT

According to current NCCN guidelines, it is not standard of care to offer sentinel node staging to patients with thin mitogenic melanomas less than 0.76 mm in Breslow thickness (MPATH DX Category 4) (11).
Melanocytic nevi are benign proliferations of melanocytes. Although some similar or related lesions may represent hamartomatous malformations, the majority of nevi are likely neoplastic in nature. In support of this assumption, nevi have been found to be clonal in limited studies. In addition, most nevi contain mutated oncogenes, the most common of which is the same oncogene, BRAF, that is found in melanomas of the superficial spreading type, the most common form of melanoma.

As was stated by Whimster (1), the definition of a melanocytic nevus relies primarily on the presence of “nevus cells.” Nevus cells, in turn, are a special class of melanocytes that have three major distinguishing properties. First, they appear to have lost the normal contact inhibition that separates melanocytes along the dermal–epidermal junction, with several keratinocytes intervening between each melanocyte. This lack of contact inhibition results in one of two characteristic patterns of melanocytic proliferations. The first of these is the “lentiginous” pattern, which is characterized by contiguous proliferation of single melanocytes. This pattern, in isolation, is seen in lentigines. The second characteristic pattern is the “nested” pattern, which by definition is required for diagnosis of a melanocytic nevus. A second major property of nevus cells that distinguishes them from normal melanocytes in the skin is a tendency for them to retain pigment in their cytoplasm rather than to transfer the pigment to neighboring keratinocytes. In Caucasian skin, melanocytes themselves are not conspicuously pigmented. Pigment, when present, tends to form a “cap” or “umbrella” of melanin above the nuclei of basal keratinocytes. The melanocytes themselves tend to be located beneath the keratinocytes, protruding into the basement membrane, and presumably protected from UV light to a greater or lesser extent depending on the amount of melanin in the keratinocytes that overlie them. The third property of nevus cells that was emphasized by Whimster is a lack of obvious dendrites. Dendrites, however, may be retained in some nevoid melanocytic proliferations and in melanomas.

Observations of the development of nevi in children, largely anecdotal, have led to the general impression that nevi develop first as a junctional proliferation of nevus cells in the epidermis. The smallest, simplest junctional proliferations exhibit a lentiginous pattern of proliferation where single cells are present near the tips and sides of elongated rete ridges, constituting a “simple lentigo” or “lentigo simplex.” Clinically indistinguishable lesions may in addition contain one or more nests of melanocytes, defined as a contiguous collection of three or more melanocytes but usually considerably more. A lesion with a few nests and a predominantly lentiginous pattern has been whimsically referred to as a “jentigo.” In any event, these lesions are typically small, symmetrical, and well circumscribed and present little or no difficulty in distinction from melanoma. Some patterns of proliferation in these lesions may overlap with mildly dysplastic nevi, to be discussed below.

1.2 Nevi Including Dysplastic Nevi
Another important property of nevus cells is their propensity to migrate from the epidermis into the dermis. It is believed that many, although probably not all nevi evolved from a junctional proliferation that is initially lentiginous (comprised of single cells), but that by definition is termed a nevus when nests of melanocytes develop among the lentiginous proliferation of single cells. The lesion is then a junctional nevus. Junctional nevus cells have a propensity to migrate from the epidermis into the dermis where they may survive indefinitely but lack the ability to proliferate because of the activity of suppressor genes such as p16 (2,3). Lesions with the predominant pattern of single cells and only a few nests may be referred to as “lentiginous junctional nevi.”

Dysplastic nevi are variants of benign nevi that are characterized by atypical architectural and cytologic features (4). The architectural features tend, to some extent, to recapitulate those of lentigines and lentiginous nevi, which are considered to be “immature” patterns of differentiation. Cytologic atypia presents as enlargement, irregularity, and hyperchromatism of scattered lesional cells, a phenomenon termed “random” cytologic atypia. Although individual cells may be quite severely atypical, these atypical cells constitute a minority population, usually less than 5%. When there is severe atypia involving greater than 50% of the population of cells, this is referred to as “uniform” cytologic atypia, increasing concern for melanoma, although other attributes would typically be required for a definitive diagnosis of melanoma, as discussed below.

Melanocytic nevi, including dysplastic nevi, and with only rare exceptions such as giant congenital nevi, which have major cosmetic significance for affected individuals in addition to being potential precursors of melanoma, are important only in relation to melanoma, in one or more of three ways:

1. Nevi are potential precursors of melanoma. However, even though 30% to 50% of melanomas may arise in association with a contiguous nevus as judged by a contiguous nevus histologically, the vastly greater number of nevi in populations at risk for melanoma indicates that this progression is very rare in terms of individual nevi (5). Therefore, it is not appropriate, for example, to attempt to prevent melanoma by excising nevi, because not only would a very large number of procedures need to be done, but also even in the best case, only perhaps a third of the melanomas would be prevented.

2. Nevi are markers of individuals at increased risk for melanoma. Numerous epidemiologic studies have related the total number of nevi, the number of large nevi, and the number of clinically atypical or dysplastic nevi to melanoma risk. This risk interacts with other factors including lentigines or “freckles,” sun exposure, evidence of solar damage, and family and prior personal history of melanoma (6). In a meta-analysis the number of large nevi and the number of dysplastic or clinically atypical nevi have been confirmed as important risk factors (7). In addition, the lesions clinically termed “freckles,” most of which are probably in fact actinic lentigines when examined histologically, are also a strong phenotypic risk factor for melanoma and interact strongly with nevi and dysplastic nevi (8). In patients with multiple risk factors, the risk for melanoma may be very high and may approach 100% lifetime risk.

3. Nevi are simulants of melanoma. While the diagnostic distinction is easy to make in the case of benign nevi, nevi with architectural disorder and cytologic atypia (dysplastic nevi), and other forms of nevi to be discussed in later sections, may be very difficult to distinguish. Clinical and histologic criteria for making this distinction are of paramount importance in the accurate diagnosis of melanoma. The distinction between a benign melanocytic nevus and a melanoma is often trivial and is made clinically every
day in examination of patients, where most nevi, of course, are not selected for biopsy. In lesions that are clinically equivocal or have features suggesting that they might be melanomas, excision and histological examination constitute the “gold standard” for melanoma diagnosis. The histologic distinction between most nevi and most melanomas is made reliably in characteristic cases. There is a relatively large number of cases, however, that present conflicting or subtle features in which the distinction is more difficult to make. In any event, the most important simulants of melanomas are melanocytic nevi, and among these simulants, dysplastic nevi constitute perhaps the largest group of most difficult cases. The features of melanocytic dysplasia overlap to some extent with those of melanomas. When these features are expressed floridly or “severely” there is a considerable degree of overlap that can lead to uncertainty. Therefore, the most severely dysplastic nevi constitute the most important simulants of melanoma and represent the most challenging cases to diagnose with specificity.

**HISTOLOGIC DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF DYSPLASTIC NEVI**

The main histologic features of dysplastic nevi include the presence of a junctional component within which there are nested and single melanocytes arranged with nests predominating, predominantly near the dermal–epidermal junction and predominantly near the tips and sides of elongated rete ridges (9,10). There are nests that bridge between adjacent elongated rete. In the dermis, there are characteristic patterns of fibroplasia called “concentric eosinophilic fibroplasia” and “lamellar fibroplasia.” These patterns of fibroplasia differ from the diffuse fibroplasia that is often seen within the papillary dermis in melanomas. There is also usually a patchy lymphocytic infiltrate. Cytologically, there is usually at least a subpopulation of more epithelioid or “type A” melanocytes, which have relatively abundant cytoplasm and often finely divided melamin pigment. There is also “random” cytologic atypia characterized by enlargement, irregularity, and hyperchromatism, with or without nucleoli, and the randomly scattered population of the lesional cells. As atypia becomes more “uniform,” concern for melanoma is increased. Mitotic figures are rare or absent in the vast majority of dysplastic nevi and their presence is concerning for melanoma. If there is a dermal component, it is centrally located, forming a “head” between two “shoulders” of junctional melanocytic dysplasia. These dermal nevus cells are usually confined to the papillary dermis, although occasionally there is a “congenital pattern” dermal component extending into the reticular dermis. They usually show evidence of maturation compared to the overlying dysplastic cells and also with descent from superficial to deeper portions of the dermal component. Sometimes cytologically atypical cells similar to those in the epidermis are present in the dermis, and if there is no evidence of proliferation in the dermis, these findings are consistent with “dermal dysplasia.” The most important differential diagnostic categories for dysplastic nevi include nondysplastic nevi and melanomas. Nondysplastic nevi that may present difficulties in distinguishing from dysplastic nevi include lentiginous junctional nevi, which have many of the architectural features of dysplastic nevi but lack cytologic atypia, and “lentiginous nevi of the elderly,” which occur on chronically sun-damaged skin in older subjects. These lesions are discussed in Section 2.2. Although Spitz nevi do not usually closely resemble dysplastic nevi, there is a category of spitzoid lesions that have a prominent junctional component and present overlapping features with dysplastic nevi (11). These are distinguished by being comprised of large spindle and/or epithelioid melanocytes with abundant amphophilic cytoplasm and large nuclei with
Attributes that may assist in distinguishing dysplastic nevi from superficial melanomas and non-dysplastic nevi are summarized in Table 1.1, based on extensive literature and on experience. In general, dysplastic nevi tend to be intermediate between the other two conditions in terms of various attributes including in particular lesional size. Dysplastic nevi tend to exhibit greater symmetry than melanomas, with a characteristic head and shoulders architecture. In dysplastic nevi, the rete ridges are characteristically uniformly elongated, with single and nested melanocytes arranged predominantly near the tips and sides of these rete and with many nests bridging between adjacent rete. The lesional cells in dysplastic nevi are nevoid, often with scattered larger more epithelioid cells, the latter resembling those of some melanomas, that present as a minority population. Two characteristic patterns of proliferation are seen in melanomas, namely lentiginous proliferation (continuous basal) and/or pagetoid proliferation (high-level scatter), and the presence (other than minimal, and focal) of either of these features in a possible dysplastic nevus is reason for concern. Cytologically, there are scattered cells in dysplastic nevi that have nuclei that are enlarged, irregular, and hyperchromatic to varying degrees ranging from mild to severe. As the proportion of these cells increases from “random” (i.e., approximately 5%) to “uniform” (i.e., 50% or more), concern increases for melanoma. In the dermis, dysplastic nevi are characterized by patterns of concentric or eosinophilic fibroplasia, whereas in melanomas diffuse fibroplasia is often seen. Regression, characterized by the absence of lesional cells often with a “footprint” of fibroplasia, is rarely seen in nevi. The dermal cells of dysplastic nevi, like those of common nevi, show evidence of maturation from superficial to deep, and mitotic figures are rare or absent.

**Grading Histologic Dysplasia—Mildly, Moderately, and Severely Dysplastic Nevi as Risk Markers for Melanoma**

It has always been evident that the histologic features of dysplastic nevi function as continuous variables, ranging from subtle to florid or from “mild” to “moderate” and “severe.” It has often been assumed that severe dysplasia is more likely to be associated with greater risk and perhaps also with progression to melanoma if not completely excised. Two relatively recent studies have looked at the relationship between degrees of histologic dysplasia and melanoma risk. In a 2003 study by Arumi-Aria et al. from Cornell, retrospective reviews of pathology reports were performed on 20,275 nevi (12). From this total, 6,275 were diagnosed as nevi with architectural disorder (dysplastic nevi), which were in 4,481 patients. These patients were then divided into those whose worst degree of dysplasia was mild (2,504), moderate (1,657), or severe (320). The records indicated that a personal history of melanoma was present in 5.7% of patients with mild, 8.1% with moderate, and 19.7% with severe atypia (dysplasia). Odds ratios for melanoma risk were 4.08 for severe versus mild, 2.81 for severe versus moderate, and 1.45 for moderate versus mild dysplasia. It was not possible to derive an odds ratio for mild dysplasia versus no dysplasia; however, inspection of the trends of the data would suggest that this difference might not be significantly different from 1. Of interest, mild dysplasia is by far the most common of the three grades. Severe dysplasia is relatively uncommon. These authors provided detailed descriptions and illustrations of differing grades of dysplasia, constituting evidence-based criteria for grading dysplastic nevi.
The study reviewed above could have some confounding biases related to its retrospective nature—for example, patients with melanoma would be more likely than others to have nevi biopsied. In a 2006 study led by Piepkorn and coworkers, a randomized prospective study was conducted in which the most clinically atypical nevus was biopsied from 80 melanoma cases and spouse controls (13). Sections were reviewed by 13 dermatopathologists who were members of the North American Melanoma Study Group. In persons with nevi receiving an average score of greater than 1 (i.e., nevi considered to have greater than mild histologic dysplasia), there was an increased risk of melanoma with an odds ratio of 2.60. This difference persisted after adjustment for confounders with an odds ratio of 3.99, 95% confidence interval 1.02 to 15.71. The interobserver reliability associated with grading histologic dysplasia was poor with a weighted kappa of 0.28; however, in a case-control format these interobserver differences were presumably controlled for.

It is of note that in both of these studies there is evidence, or at least a suggestion, that mild histologic dysplasia is not associated with increased melanoma risk. Conversely, moderate dysplasia and especially severe dysplasia are associated with quite high risk, comparable to that associated with clinically dysplastic nevi reviewed above. Interobserver reliability was poor in the study of Piepkorn and coworkers, likely because observers used subtly different thresholds for their criteria, as has been demonstrated in the past. Agreement on the most efficient criteria could likely improve this reliability; however, other data suggest that distinction between mildly dysplastic and nondysplastic junctional nevi may be difficult to make.

Although it has been stated that dysplastic nevi are very common or almost ubiquitous in general populations (14), the statement may have some validity for mild dysplasia but not for moderate or severe dysplasia. In the Cornell study, 55% of the patients with histologic dysplasia had mild dysplasia, while the dysplasia was moderate in 37% and severe in 7% of these patients. The 6,275 histologically dysplastic nevi in the study represented 31% of the total number of 20,275 nevi examined during the study. From these data it can be inferred that moderate and especially severe dysplasia are relatively rare entities. These are associated with significantly increased relative risks for future development of melanoma. Conversely, mildly dysplastic nevi are relatively common and do not appear to be associated with significant melanoma risk.

These considerations would suggest that mild dysplasia should perhaps be abandoned as a clinically useful term, much as has been done with “prostatic intraepithelial neoplasia grade I” (“PIN I”) in the prostate. By general agreement, this term is no longer used because it is poorly reproducible and is not associated with risk of cancer, properties that seem to be shared by mildly dysplastic nevi.

MANAGEMENT OF NEVI AND DYSPLASTIC NEVI

It is natural to suppose that severely dysplastic nevi might be more likely to undergo progression than moderately or mildly dysplastic lesions. This is not a study that can be ethically done. There are limited studies that suggest that incompletely excised dysplastic nevi do not recur or progress to melanoma, although it is not clear whether these studies have included an appreciable number of severely dysplastic nevi (15). In addition, there is overlap between the criteria for severe melanocytic dysplasia and melanoma in situ, such that there is often some degree of uncertainty as to the diagnosis. In addition, if a lesion is present on the specimen margin, it has not by definition been completely examined in order to rule out possible focal changes of melanoma.
Therefore, most dermatopathologists, and most clinicians, recommend complete reexcision for an incompletely excised severely dysplastic nevus. Opinions vary regarding moderately dysplastic nevi, and most would agree that mildly dysplastic nevi, and common acquired and small congenital pattern nondysplastic nevi do not warrant complete excision, even if a margin is positive.

In terms of the MPATH DX reporting system, most common acquired nevi and mildly dysplastic nevi will be MPATH DX Category 1, moderately dysplastic nevi may be MPATH DX Category 1 or Category 2, and severely dysplastic nevi are usually MPATH DX Category 2, or possibly Category 3 (excision with 5 mm margins) if there is serious concern for a differential diagnosis of melanoma in situ.

**CLASSIFICATION OF NEVI IN TERMS OF SOLAR DAMAGE**

In terms of the “CSD” classification of melanoma, most dysplastic nevi in our experience are in the “no CSD” or “low CSD” category. Common acquired dermal nevi, often with congenital pattern features, may be identified in chronically sun-damaged skin, but they may well have arisen during the younger layers of life when solar damage was less severe or absent. Dysplastic nevi, like other acquired nevi, commonly have mutations of the oncogene BRAF (16).

**References**

1.2.1

Epithelioid Cell Melanocytic Dysplasia Versus Superficial Spreading Melanoma

CLINICAL INFORMATION
Lesion of the back in a 60-year-old man.

REASON FOR CONSULTATION
I am concerned about the possibility that this lesion is a melanoma arising in a nevus.

FIGURE 1.2.1.1 Scanning magnification shows a broad lesion that is moderately cellular and generally symmetrical, but with some variation of architecture from side to side across the lesion.

FIGURE 1.2.1.2
FIGURES 1.2.1.2 and 1.2.1.3 The lesion is comprised of relatively large nevoid to epithelioid melanocytes arranged in nests mainly near the tips and sides of elongated rete ridges. There is a patchy to focally brisk lymphocytic infiltrate in the dermis.
1.2.1

**DESCRIPTION**

These sections show a shave biopsy of skin, containing a moderately to focally more highly cellular proliferation of relatively large epithelioid melanocytes, arranged predominantly in nests, predominantly near the dermal–epidermal junction, with some nests bridging between adjacent elongated rete ridges. In the dermis, there is concentric eosinophilic fibroplasia and a patchy lymphocytic infiltrate with melanophages. This lesion presents somewhat discordant features, namely architectural features of a dysplastic nevus with a somewhat unusual epithelioid cell cytology overlapping with cytologic features of some melanomas. Nuclear atypia, however,
is mild to moderate rather than moderate to severe and mitotic figures are rare or absent. Cells that are present in the dermis appear to mature along nevic lines. I would therefore consider this lesion to be benign albeit severely dysplastic and would characterize it as follows:

**COMMENT**

The diagnosis of severe dysplasia is based on architectural features as well as cytologic features. Because of the severe dermal and epidermal dysplasia and differential diagnosis of melanoma, I would recommend an additional procedure to be sure this lesion has been completely removed with, at a minimum, a margin of normal skin around the scar of this procedure and any residual lesion. Follow-up for the patient may also be appropriate.

**OVERALL COMMENT**

This lesion demonstrates a pattern that has been described as epithelioid melanocytic dysplasia in which the predominant cell type has abundant cytoplasm and finely divided “dusty” cytoplasmic melanin pigment. This cytology to some extent resembles that of many melanomas of the superficial spreading type. In this case, cytologic atypia is of lesser degree than would be expected and most melanomas. This is an MPATH Category 2 or perhaps Category 1 lesion, the latter especially perhaps if the patient has already had many excisions and is likely to be carefully followed.
1.2.2

Moderate Versus Severe Dysplasia

CLINICAL INFORMATION
Please find enclosed slides on a 36-year-old male with multiple dysplastic nevi removed.

REASON FOR CONSULTATION
I have also enclosed a prior pathology report of other lesions removed. My diagnosis is compound melanocytic nevus with architectural disorder and moderate cytologic atypia. However, I am concerned that this lesion may be severely dysplastic. Would you recommend a reexcision procedure?

DESCRIPTION
Sections show a moderately cellular proliferation of nevoid to epithelioid melanocytes arranged singly and in nests in the epidermis, with nests predominating. These are arranged predominantly near the dermal–epidermal junction, predominantly near the tips and sides of elongated rete ridges, with some bridging nests. There is no extensive high-level pagetoid scatter into the epidermis. Cytologically, randomly scattered lesional cell nuclei are moderately enlarged and slightly and irregular and hyperchromatic, consistent with moderate random cytologic atypia. Lesional cells in the dermis show evidence of maturation along nevic lines. The lesion appears to be excised in the section planes available for study.

FIGURE 1.2.2.1 A broad, symmetrical, moderately cellular lesion.

FIGURE 1.2.2

FIGURES 1.2.2.2 and 1.2.2.3 Left and right halves of the lesion demonstrate symmetry with junctional “shoulders” and reasonably good circumscription.
1.2.2

**FIGURE 1.2.2.4** There are nests near the dermal–epidermal junction with bridging between adjacent elongated rete ridges. Scattered lesional cells have moderately enlarged nuclei.

**FIGURE 1.2.2.5** There is a dermal component that shows evidence of maturation along nevic lines.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin, back: Compound nevus with moderate dysplasia, completely excised, see Description and Comment.</strong></td>
</tr>
</tbody>
</table>

**COMMENT**

This patient presents with multiple lesions, some of which are dysplastic nevi with moderate dysplasia. These are benign lesions with little or no potential for recurrence and no potential for metastasis. Periodic follow-up may be appropriate for this patient, especially if there are other clinically atypical nevi and/or a family or personal history of melanoma. Although the lesion extends close to the specimen margin, there is no essential indication for reexcision, especially if the patient is to be followed.

**OVERALL COMMENT**

Dysplasia in this lesion is mild to moderate. It is relatively broad, moderately cellular, and lacks severe uniform cytologic atypia or architectural features concerning for evolving melanoma in situ. This is an MPATH DX Category 1 or perhaps Category 2 lesion, depending on clinical correlation and preference.
1.2.3

Mild Dysplasia Versus Junctional Nevus

CLINICAL INFORMATION
A macular slightly variegated lesion from the back of a 37-year-old woman.

REASON FOR CONSULTATION
Is this a dysplastic nevus?

DESCRIPTION
These sections show a small skin biopsy, containing a moderately cellular proliferation of nevoid melanocytes, measuring 2 to 3 mm in diameter on the slide. The lesional cells are arranged mainly around the tips and sides of elongated rete ridges, as single cells and a few nests. There are focal bridging nests. There is focal mild enlargement of scattered lesional cell nuclei. There is no pagetoid scatter, and no extensive continuous proliferation between the rete. In summary, I would interpret this lesion as follows:

FIGURE 1.2.3.1 A broad, sparsely to moderately cellular, symmetrical lesion.

FIGURE 1.2.3.2

FIGURES 1.2.3.2 and 1.2.3.3 Left and right sides of the lesion demonstrate that it is not especially well circumscribed. The cellularity is low. There is a patchy lymphocytic infiltrate with melanophages in the dermis.
1.2.3

**DIAGNOSIS**

Skin, abdomen: Lentiginous compound nevus, with mild dysplasia, see Description and Comment.

**COMMENT**

As discussed above, this lesion has features of a mildly dysplastic nevus. I see no evidence of malignancy. The lesion appears to be excised; however, even if this were not the case, reexcision might not be necessary if this biopsy was considered representative of the lesion and especially if the patient were to be followed. Mild dysplasia is not an independent risk factor for melanoma; however, if this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, or other melanoma risk factors, consideration of periodic surveillance may be appropriate.

**OVERALL COMMENT**

Since mild dysplasia is not an independent risk factor for melanoma, lesions of this type might be better given a descriptive name such as “lentiginous junctional nevus.” It is important to distinguish these lesions from nevoid lentigo maligna, which can also be characterized by slight degrees of cytologic atypia. This is an MPATH Category 1 lesion (no need for reexcision, even if margins are positive).
CLINICAL INFORMATION
A variegated pigmented lesion on the back of a 29-year-old man.

REASON FOR CONSULTATION
Is this a nevoid melanoma?

DESCRIPTION
These sections show a shave biopsy of skin, containing a generally moderately cellular proliferation of nevoid to epithelioid melanocytes, arranged singly and in nests, with nests generally predominating, predominantly near the dermal–epidermal junction. There are many nests bridging between adjacent elongated rete ridges. These architectural features are those of a dysplastic nevus. In addition, however, there are several foci of pagetoid scatter into the epidermis, focally near the stratum granulosum, and there is moderate to severe relatively uniform cytologic atypia in the form of nuclear enlargement and hyperchromatism. Cells similar to those in the epidermis protrude into the papillary dermis in the form of small nests without tumorigenic or mitogenic activity. Maturation is incomplete, however, with some cells near the base of the lesion having enlarged hyperchromatic nuclei with nucleoli. Although the presence of foci of pagetoid scatter raises significant question of evolving melanoma in situ, the absence of tumorigenic proliferation and mitotic activity in the dermal component are more reassuring features. The diffuse fibroplasia associated focally with the dermal component is similar to that which has been described in fibrosing dysplastic nevi. An HMB 45 stain demonstrates a top-heavy staining pattern. Taking these findings together, I would agree that the diagnosis of melanoma is not fully supported in this case and would characterize it as follows:

FIGURE 1.2.4.1 A broad and moderate to markedly cellular lesion with a somewhat asymmetrical architectural profile.
FIGURE 1.2.4.2 The lesion is reasonably well circumscribed at its periphery. Cells in the epidermis are present as nests predominating over single cells, predominantly near the dermal–epidermal junction.

FIGURE 1.2.4.3 and 1.2.4.4 There is a dermal component comprised of nevoid cells that shows some evidence of maturation but nevertheless have somewhat enlarged hyperchromatic nuclei. There is also an associated lymphocytic response. Note the presence of fibroplasia in the dermis, which could suggest the possibility of trauma or perhaps a stromal response.
1.2.4

**Figure 1.2.4.5** HMB 45 staining demonstrates a generally “top-heavy” pattern.

**Figure 1.2.4.6** In this field, the dermal cells stained with HMB 45 and pagetoid scatter is identified in the junctional component.

**Figure 1.2.4.7** In this field, the dermal nevus cells are negative with HMB 45.

**Diagnosis**

Skin, right upper back: Compound nevus with severe dermal and epidermal dysplasia, apparently excised, see Description and Comment.

**Comment**

As noted above, the differential diagnosis could include a lesion with focal evolving melanoma in situ. I do not favor this diagnosis and in particular, I do not believe the dermal component is melanoma. The lesion appears to be minimally excised with changes in the epidermis approaching less than 1 mm of the specimen margin. Because of the severe atypia I would recommend consideration of periodic follow-up for this patient, and this would be especially important if he should have other clinically atypical nevi and/or a family or personal history of melanoma.

**Overall Comment**

This lesion is characterized as severely dysplastic primarily because of the presence of severe cytologic atypia, which is present in dermal as well as in junctional cells, and also because of the presence of low-level pagetoid scatter (a “severe” architectural feature). This is an MPATH DX Category 2 or Category 3 lesion. Given that the lesion is already excised, it could be appropriate to follow the lesional site if the patient is likely to be compliant with follow-up recommendations.
**CLINICAL INFORMATION**
A pigmented lesion from the calf of a 22-year-old woman.

**REASON FOR CONSULTATION**
I am concerned about melanoma arising in a dysplastic nevus.

**DESCRIPTION**
These sections show a broad, plaquelike lesion, characterized at its periphery by a junctional component, forming a shoulder to a central portion where lesional cells extend from the epidermis into the papillary dermis, expanding it, and extending into upper reticular dermis collagen fiber bundles. In the junctional component, the cells are predominantly arranged in nests, predominantly near the dermal–epidermal junction, with many nests bridging between adjacent elongated rete ridges. In the central compound portion, there is evidence of maturation of lesional cells from superficial to deep. An occasional junctional lesional cell mitosis is observed, which I agree is a concerning feature; however, in the absence of extensive high-level pagetoid scatter or continuous basal lentiginous proliferation, or more severe uniform atypia, I do not believe this lesion is likely to be a melanoma; however, there are some concerning features including a tendency to confluence of nests.

**FIGURE 1.2.5.1** A broad, moderately cellular lesion with a symmetrical distribution of junctional “shoulders” around a central dermal component.
and moderate to rather severe atypia, as well as the mitotic activity, and I will therefore interpret it to some extent descriptively as follows:

**Figure 1.2.5.2** At one periphery, the lesion is reasonably well circumscribed.

**Figure 1.2.5.3** There is moderate to severe cytologic atypia of junctional and superficial dermal lesional cells.

**Figure 1.2.5.4**

**Figure 1.2.5.5**

**Figures 1.2.5.4 and 1.2.5.5** The central dermal component also demonstrates severe atypia, and poor maturation from superficial to deep. In addition, a mitotic figure (not shown) was seen in this area.
1.2.5

**Figure 1.2.5.6** HMB 45 staining shows a “top-heavy” pattern, with strong staining in the junctional component and superficial dermal component, and lesser staining in the deep dermal component.

**Figure 1.2.5.7** Ki-67 staining is essentially negative.

**Figure 1.2.5.8** Staining for p16 shows a characteristic “checkerboard” pattern, seen in many benign nevi.

**Diagnosis**

Skin, right calf: Compound nevus with severe dermal and epidermal dysplasia, with junctional mitotic activity of uncertain significance, see Description and Comment.
COMMENT

COMMENT 1

One might consider ancillary studies such as fluorescence in situ hybridization or comparative genomic hybridization for a lesion of this type. Based on a recent study by Gerami et al., which demonstrated that homozygous 9p21 loss was the only genomic finding independently associated with aggressive behavior, I now believe that p16 staining can be helpful as a preliminary test. If p16 staining is positive, then homozygous 9p21 loss cannot have occurred and this would be a reassuring finding. I would be happy to have the stain performed in our laboratory, if you would care to have this done and send us the block. At the same time, the Ki-67 study to assess dermal proliferation and an HMB 45 stain to assess maturation can be helpful in lesions of this type, with atypia of the dermal component. If p16 staining is negative, then comparative genomic hybridization could be a reasonable option to consider.

COMMENT 2 (A FEW DAYS LATER)

Immunostains have been completed. The lesion is “top-heavy” with HMB 45, which stains the junctional component and a few cells of the superficial dermal component. Ki-67 appears to stain a few junctional cells, as might be expected given the prior finding of a rare junctional mitosis. Only a few positive cells are present in the dermal component and these are most consistent with lymphocytes. Positive staining for p16 in a checkerboard pattern in the immature cells is consistent with benign melanocytic proliferations. The more mature cells at the base of the lesion are negative with p16, as one would expect. These findings support a benign interpretation of this lesion as a compound nevus with severe dermal and epidermal dysplasia, with mitotic activity.

OVERALL COMMENT

Given the differential diagnosis of melanoma, which is not entirely excluded, this lesion could be treated as an MPATH Category 3 or Category 4 lesion.
1.2.6

Severe Dysplasia Versus Melanoma In Situ

**Clinical Information**
Clinical impression: rule out congenital nevus in a 19-year-old female.

**Reason for Consultation**
Reason for referral: Compound nevus, congenital type, with moderate to severe architectural disorder and focal random cytologic atypia. Supra basal melanocytes are noted. The lesion appears to be completely excised on the sections studied, although approaches the lateral margins of some sections. A reexcision is warranted to assure its complete removal. A second opinion will be obtained.

![Figure 1.2.6.1](image1.png) **Figure 1.2.6.1** A broad, superficial lesion with a generally symmetrical architectural profile.

![Figure 1.2.6.2 and 1.2.6.3](image2.png) **Figure 1.2.6.2** and **Figure 1.2.6.3** The lesion extends to one peripheral margin. It is comprised of single and nested melanocytes arranged with nests predominating, predominantly near the dermal–epidermal junction, and bridging between adjacent elongated rete ridges. There is concentric fibroplasia beneath the rete and there is a patchy lymphocytic infiltrate in the dermis.
**DESCRIPTION**
These sections show a shave biopsy of skin containing a fairly broad, plaquelike, moderately cellular melanocytic lesion comprised of epithelioid to spindle-shaped melanocytes arranged predominantly in nests, predominantly near the dermal–epidermal junction, with many nests bridging between adjacent elongated rete ridges. Cytologically, there is moderate to focally severe enlargement, irregularity, and hyperchromatism of scattered lesional cell nuclei consistent with moderate to severe random cytologic atypia. In the center of the lesion, there are orderly nevus cells extending into the papillary dermis showing evidence of maturation from superficial to deep without tumorigenic proliferation or mitotic activity. In summary, I would agree with your diagnosis as follows:

**DIAGNOSIS**
Skin, left upper back: Compound nevus with moderate to severe dysplasia, extending to a specimen margin, see Description and Comment.

**COMMENT**
Because of the moderate to severe dysplasia one might consider an additional procedure to be sure this lesion has been completely removed, or perhaps careful follow-up of the lesional site.

**OVERALL COMMENT**
There is no evidence of frank malignancy in this lesion. Interestingly, it recurred 2 years later as an example of “recurrent nevus phenomenon,” with no evidence of malignancy (see Case 1.3.1). This recurrence was benign. This lesion would be best interpreted prospectively as an MPATH DX Category 2 lesion. It is not clear whether a reexcision procedure was performed in this case or not.
1.2.7

**Fibrosing Dysplastic Nevus Versus Melanoma With Regression**

**CLINICAL INFORMATION**

An irregular pigmented lesion on the back of a 59-year-old man.

**REASON FOR CONSULTATION**

Is this a nevoid melanoma?

**FIGURE 1.2.7.1** A broad lesion with a fibrotic dermal component within which there are multiple clusters of small dark cells.

**FIGURE 1.2.7.2**

**FIGURES 1.2.7.2 and 1.2.7.3** The cells in the dermis have a nevoid appearance. In the overlying epidermis, there is an increased number of single and nested melanocytes with moderate nuclear variability.
**FIGURE 1.2.7.4** HMB 45 staining is “top heavy.”

**FIGURE 1.2.7.5** Ki-67 staining is minimal or absent in the dermal cells. There are a few positive controls in keratinocytes.

**FIGURE 1.2.7.6** Immunostaining for p16 labels cells in a “checkerboard” pattern that is characteristic of benign but atypical nevoid lesions such as Spitz tumors (the expected pattern in fully mature nevus cells is negative as these cells have completed oncogene-mediated senescence).

**DESCRIPTION**

These sections show a shave biopsy of skin, containing a broad lesion characterized at its periphery by a junctional component, containing single and nested melanocytes, with some bridging between adjacent elongated rete ridges and with generally moderate random atypia. In another area, there is a dermal component, characterized by variably sized, often quite large nests and small nevoid melanocytes, embedded in a fibrous stroma. Above this dermal component there is diffuse fibroplasia, and in the epidermis there is a tendency to confluence and pagetoid scatter of cells into the epidermis, although generally not beyond the lower third. There is also a somewhat greater degree of somewhat more uniform cytologic atypia; however, in the absence of more extensive high-level...
1.2.7

I tend to favor a fibrosing dysplastic nevus, as has been described in several studies recently in the literature (17). There is a suspicion that these changes may be related to trauma, in which case the junctional component could be considered analogous to the so-called “recurrent nevus phenomenon.” In order to perhaps resolve these competing possibilities, I would suggest additional special stains, including HMB 45 to assess maturation, and Ki-67 and p16 to assess the proliferative potential, especially of the dermal component. We would be happy to perform the stains in our laboratory if you would care to send us the block.

COMMENT

COMMENT 1

I tend to favor a fibrosing dysplastic nevus, as has been described in several studies recently in the literature (17). There is a suspicion that these changes may be related to trauma, in which case the junctional component could be considered analogous to the so-called “recurrent nevus phenomenon.” In order to perhaps resolve these competing possibilities, I would suggest additional special stains, including HMB 45 to assess maturation, and Ki-67 and p16 to assess the proliferative potential, especially of the dermal component. We would be happy to perform the stains in our laboratory if you would care to send us the block.

COMMENT 2 (A FEW DAYS LATER)

Immuno stains have been completed. The HMB 45 stain demonstrates a “top-heavy” pattern with minimal staining of the dermal component. The Ki-67 stain is completely negative in the dermal component. The p16 stain demonstrates a brightly positive “checkerboard” pattern of staining in the dermal component. These findings support a benign interpretation. I would therefore interpret this lesion as follows:

DIAGNOSIS

Skin, right, midback: Melanocytic tumor of uncertain malignant potential, see Description and Comment.

I would recommend consideration of an additional procedure to be sure this lesion has been completely removed, or perhaps alternatively, careful follow-up of the lesional site. Especially if this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance of his skin would also be appropriate.

FINAL DIAGNOSIS

Skin, right, midback: Compound nevus with severe dermal and epidermal dysplasia and dermal fibrosis (“fibrosing dysplastic nevus?”), extending close or to specimen base and margins, see Description and Final Comment.

The presence of p16 staining rules out the possibility of 9p21 loss, which has been associated with aggressive behavior in a recent fluorescence in situ hybridization (FISH) study of atypical lesions, most of which were variants of Spitz tumors (18). Despite the reassuring findings from special stains, this is objectively an atypical lesion, and complete excision would be recommended (MPATH DX Category 2 or 3).
1.2.8

Dysplastic Nevus or Not?

**CLINICAL INFORMATION**
A 10 cm lesion with speckled brown pigmentation on the thigh in an 11-year-old girl.

**REASON FOR CONSULTATION**
This lesion is clinically a nevus spilus. Is there significant atypia?

**DESCRIPTION**
Sections show a very broad excision biopsy of skin, containing a variably cellular but generally sparsely to moderately cellular proliferation of nevoid melanocytes. These are arranged as single cells predominantly and also as nests within the epidermis. There is variable pigmentation. In some areas there is pagetoid scatter of lesional cells into the epidermis generally not beyond the middle third. There are multiple foci where mature dermal nevus cells are present, mostly in the form of small nests. There is no substantial cytologic atypia. The lesion appears to be completely excised.

**FIGURE 1.2.8.1** The very broad skin excision specimen.

**FIGURE 1.2.8.2** There is a melanocytic proliferation that is poorly circumscribed at its periphery.
1.2.8

FIGURE 1.2.8.3

FIGURES 1.2.8.3 and 1.2.8.4 The proliferation is quite variable intensity. There are suprabasal melanocytes. There are also clusters of nevoid cells in the dermis.

FIGURE 1.2.8.5 There is no substantial cytologic atypia.

DIAGNOSIS
Skin, back: Lentiginous compound nevus with congenital pattern features consistent with nevus spilus.

COMMENT
I see no evidence of malignancy in this material.

■ OVERALL COMMENT ■

Nevus spilus is a benign diagnosis. These lesions may be considered analogous to congenital nevi. There are numerous mostly single case reports of melanomas and also of Spitz tumors arising in nevus spilus; however, these do not appear to be especially high-risk precursors (19–22). Complete excision if possible is reasonable management, or if not, follow-up (MPATH DX Category 1 or 2).
1.2.9

Severe Dysplasia Versus Melanoma

**CLINICAL INFORMATION**

A 44-year-old woman with an irregular pigmented lesion of the back, rule out melanoma.

**REASON FOR CONSULTATION**

I favor a severely dysplastic nevus but cannot rule out melanoma.

**DESCRIPTION**

These sections show a shave biopsy of skin containing a moderately cellular proliferation of nevoid to epithelioid melanocytes arranged mostly in nests, along the dermal–epidermal junction, with nests bridging between adjacent elongated rete ridges. Cytologically, there is moderate to severe atypia of lesional cell proliferation.

**FIGURE 1.2.9.1** A broad lesion with irregularly distributed nests of nevoid to epithelioid melanocytes near the dermal–epidermal junction and in the superficial dermis.

**FIGURE 1.2.9.2**

**FIGURE 1.2.9.3**

**FIGURES 1.2.9.2 and 1.2.9.3** The lesion is rather poorly circumscribed at its left and right peripheries.
FIGURES 1.2.9.4 and 1.2.9.5 There are nests located mainly near the tips and sides of elongated rete ridges, with nests bridging between adjacent rete and with concentric and focally diffuse fibroplasia in the papillary dermis. There are no mitoses. There is also a patchy lymphocytic infiltrate in the dermis.

FIGURE 1.2.9.6 Lesional cells demonstrate moderate to severe cytologic atypia in the form of nuclear enlargement, irregularity with small nucleoli but without marked hyperchromasia and without mitotic activity.

FIGURE 1.2.9.7 Melan-A staining demonstrates irregularly spaced nests in the epidermis and in the dermis.
nuclei. This is in the form of nuclear enlargement, irregularity, and prominent nucleoli. Nevertheless, the cells are arranged in small nests that are relatively uniform in size, shape, and distribution, and there is some evidence of maturation from superficial to deep. Despite the relatively small size of this lesion, because of its architectural features and cytologic atypia, I would characterize it as follows:

**DIAGNOSIS**

Skin, back: Compound nevus with moderate to severe dysplasia, present at specimen margins, see Description and Comment.

**COMMENT**

Because of the severe dysplasia manifested principally by severe cytologic atypia without marked architectural disorder, and the positive margins, I would recommend an additional procedure to be sure this lesion has been completely removed, to rule out additional pathology, and to preclude any possibility of persistence, recurrence, and progression of this atypical lesion (MPATH DX Category 2).

**OVERALL COMMENT**

This lesion is not a characteristic dysplastic nevus; however, I believe it is best managed in that context. One might also consider a so-called “special site nevus”; however, this lesion does not present from such a site. Complete local excision is appropriate for lesions of this type (MPATH DX Category 2).
1.2.10

Fibrosing Dysplastic Nevus Versus Regressing Melanoma

**CLINICAL INFORMATION**
21-year-old female, right upper abdomen, no provided history of trauma.

**REASON FOR CONSULTATION**
Atypical compound nevus traumatized versus MIS arising in an atypical compound nevus.

**FIGURE 1.2.10.1** A broad lesion with a superficial component distributed more or less symmetrically as “shoulders” around a central dermal component. The overlying epidermal rete ridge pattern is effaced in the center.

**FIGURE 1.2.10.2** The lesion is well circumscribed at its periphery with the last cells in a well-defined nest.

**FIGURE 1.2.10.3** In the center of the lesion, the rete ridge pattern is effaced and there is superficial fibroplasia. Nests of large nevoid to epithelioid melanocytes are trapped in the fibroplasia.
DESCRIPTION

These sections show a skin biopsy containing a relatively broad, generally moderately cellular proliferation of nevoid to epithelioid melanocytes, present as nests and relatively few single cells, predominantly near the dermal–epidermal junction. There are many nests that bridge between adjacent elongated rete ridges. Cytologically, there is moderate to focally severe atypia of scattered lesional cells in the junctional component. Similar cells are present in the papillary dermis, again showing relatively random severe cytologic atypia superficially and showing considerable evidence of maturation from superficial to deep. These cells are arranged in nests that tend to be relatively large and these are embedded in a fibrous stroma. This finding raises the possibility of a traumatized nevus, and also fits reasonably well into the category of sclerosing nevi described by several groups. I generally consider this pattern of sclerosis to represent a stromal reaction to the lesional cells; however, another possibility would be trauma. In any event, I do not see convincing evidence of malignancy in this lesion and would characterize it as follows:

DIAGNOSIS

Skin, right upper abdomen: Compound nevus with severe dermal and epidermal melanocytic dysplasia, and dermal sclerosis, present at specimen base and margins, see Description and Comment.
1.2.10

**COMMENT**

Because of severe architectural disorder and cytologic atypia in this lesion I would recommend an additional procedure to be sure it has been completely removed, not only to rule out any additional pathology and allow for complete assessment of the lesion, but also to preclude any possibility of persistence, recurrence, or possible future progression of it (MPATH DX Category 2).

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**OVERALL COMMENT**

These lesions, which have been described as “sclerosing nevus with pseudomelanomatous features” or “nevus with regression-like fibrosis” (17,23) or “nevi with florid fibroplasia” (24) seem to be benign. Nevertheless they cause concern because of the diffuse fibrosis that is a characteristic of many melanomas, and the presence of immature melanocytes in the dermis. It is possible that the fibrosis is related to trauma; however, there is usually no such history. It is also possible that the fibrosis is a stromal reaction, which is probably also the case in the diffuse fibroplasia that characterizes melanomas.
1.3 Recurrent and Traumatized Nevi

Melanocytic nevi, of course, occur on the skin where they are subject to trauma. It is common to see fibroplasia in the superficial portion of nevi, and this finding may suggest the possibility of prior trauma to the surface of the nevus. One occasionally observes enlarged nevoid to epithelioid melanocytes in the epidermis above the nevus, which may represent a reactive phenomenon.

The “recurrent nevus phenomenon” was described by Kornberg and Ackerman in 1975 (1), and appears to represent perhaps a special case of traumatized nevus. The original report included cases that had been seen in consultation by Wallace H. Clark, Jr who had first identified this phenomenon. In the recurrent nevi, there may be markedly atypical junctional proliferation, which may include a few cells in the dermis. These changes may suggest melanoma and were referred to as “Pseudomelanoma.”

An important clue to the diagnosis is the fact that the proliferation remains confined to the epidermis above the scar. This relationship suggests that the “recurrent nevus” may in fact be a form of atypical melanocytic hyperplasia, likely arising from melanocytes participating in the reconstitution of the epidermis following the biopsy injury. In any event, it is concerning when atypical melanocytes are present in the epidermis adjacent to the scar of a prior procedure. Of course, if the prior procedure were a partial biopsy there would be residual elements of the original lesion present in the adjacent epidermis. This adjacent proliferation therefore needs to be evaluated on its own merits, whether representing a dysplastic process, or melanoma, in situ or invasive. As a rule of thumb, recurrent nevi occur rapidly within a matter of weeks to a few months. Paradoxically, recurrent melanoma, occasionally seen following a missed diagnosis or inadequate therapy, does not generally present until a year or more after the biopsy procedure. This phenomenon is not generally seen following traditional wide local excisions of melanomas, and usually is seen following a shave biopsy of a banal compound or dermal nevus, or a dysplastic nevus.

In a recent study (2), the clinical findings and histologic changes in 357 cases of recurrent nevus phenomenon were compared with 34 cases of melanoma with fibrosis resulting from regression, which was defined as tumor absence with extensive fibrosis and telangiectasia, melanophages, and epidermal effacement. The recurrent nevi tended to occur in young females and the back was the most common site. The recurrence typically occurred within a few months of the biopsy procedure. In the recurrent nevi, the melanocytic proliferation could be junctional or compound, and the epidermal rete could be effaced or preserved. Melanomas with fibrosis resulting from regression had overlapping features with recurrent nevi. Atypical features that could be seen in recurrent nevi included nests and single cells in the epidermis, pagetoid spread, confluent growth, adnexal spread, and inflammation. Atypical cells could also be present within the dermal scar. Residual nevus was often seen deep to the biopsy scar. Histologically, the vast
A majority of recurrent nevi were readily identifiable; however, partial biopsies or cases without prior knowledge of the original biopsy have been known to lead to misdiagnosis. It is particularly difficult to exclude melanoma with regression when the scar extends to both margins of a biopsy specimen, precluding evaluation of the normal skin peripheral to the recurrent lesion. Underdiagnosis of a regressing melanoma as a recurrent nevus is also possible. Correlation with the clinical findings and review of the prior biopsy are very important to avoid these pitfalls.

**MANAGEMENT OF TRAUMATIZED NEVI WITH ATYPIA AND RECURRENT NEVI**

Most of these lesions should be completely excised with narrow margins to rule out additional pathology that could influence the diagnosis (MPATH DX Category 2).

**References**

1.3.1

Recurrent Nevus Versus Melanoma

**CLINICAL INFORMATION**

Recurrent pigmentation at the site of prior biopsy of a nevus (approximately 8 weeks), from the back of a 19-year-old woman.

**REASON FOR CONSULTATION**

We received a wider excision of a pigmented skin lesion from the back of the above-captioned patient. The previous biopsy had been referred to you. In our residual lesion, we see atypical melanocytic proliferation with some transepidermal migration and a few mitotic figures in intraepidermal melanocytes. We are wondering whether this represents a small focus of superficial spreading melanoma or just changes in an atypical compound nevus that has been previously biopsied. At this time the lesion appears to be completely excised. However, if you think that this may be melanoma, do you think the margins are adequate?

**DESCRIPTION**

These sections show a punch biopsy of skin, containing an area of superficial fibroplasia that extends across the entire specimen. Within this area of fibroplasia, more or less centrally placed in the punch biopsy specimen, there is a moderately to highly cellular proliferation of nevoid to larger more epithelioid melanocytes arranged singly and in nests in the epidermis, mostly near the dermal–epidermal

**FIGURE 1.3.1.1** There is a broad scar in the superficial dermis that extends to both borders of the specimen. Within the region of scarring, there is a proliferation of pigmented melanocytes in the epidermis and in the superficial dermis, within the scar. This proliferation does not extend to the borders of the biopsy specimen; however, the periphery of the scar itself is not available for evaluation.

**FIGURE 1.3.1.2** The cells in the epidermis are arranged as nests, comprised of large epithelioid cells with abundant cytoplasm, and abundant cytoplasmic pigment. The nuclei are small and dark without marked pleomorphism.
section 1.3: recurrent and traumatized nevi

1.3.1

FIGURE 1.3.1.3 and 1.3.1.4 There are also single cells in the atypical junctional proliferation and there is pagetoid scatter mostly to the lower third with some few cells above this level.

FIGURE 1.3.1.5 In this region, there is pagetoid scatter into the epidermis. Cytologic atypia is mild, although the abundant cytoplasm and finely divided pigment are not typically seen in usual benign nevus cells.

the form of nests, which vary somewhat in size and shape. Most of the nests are quite small, however, and comparable in size to the largest nests in the epidermis. There are a few scattered mitoses, most of which are in the junctional component and most of which I believe are in keratinocytes. I did not see any dermal mitotic figures. Cytologically, the cells in the epidermis and in the dermis have abundant cytoplasm with abundant melanin pigment in the form of fine to intermediate melanin granules. The nuclei tend to be relatively small, or moderately enlarged, with only slightly irregular nuclear membranes, and homogeneous finely divided chromatin, some with prominent nucleoli. These could be characteristics of reactive nuclei, although in other contexts they could be consistent with moderate to severe dysplasia or melanoma. Given the occurrence of this proliferation in the epidermis and superficial dermis confined to an area of scarring of a prior shave biopsy of the nevus, I believe these changes are consistent with the so-called “recurrent nevus phenomenon,” also referred to as “persistent nevus.” In my view,
these changes actually represent a true recurrence of pigmentation at the site of the lesion rather than a persistence, and may represent a form of reactive atypical hyperplasia rather than true neoplasia. In any event, this is an atypical finding, which was termed “pseudomelanoma” in its initial description, and remains difficult to distinguish with certainty. I will therefore interpret these changes as follows, to some extent provisionally pending complete excision of this entire process.

**DIAGNOSIS**

Skin, back: Atypical intraepidermal and superficial dermal melanocytic proliferation in association with a scar, most consistent with recurrent nevus phenomenon, completely excised but with the associated scar extending to specimen margins, see Description and Comment.

**COMMENT**

I have reviewed the prior material, which shows only the changes as previously described of a compound nevus with moderate to severe dysplasia, present at a specimen edge. Since this present reexcision does not include the periphery of the scar, it is not possible to determine whether there is any persistence or recurrence of this nevus at the periphery of the specimen and I would therefore recommend another procedure, to make sure that this whole process has been removed with, at a minimum, a margin of normal skin around the scar of this and the prior procedure, and any residual lesion.

**OVERALL COMMENT**

The original lesion has been previously presented in Section 1.2.6. This was interpreted as a moderately to severely dysplastic nevus. There was a positive margin. Nevertheless, the pattern of recurrence here is not that of recurrence of a junctional nevus or melanoma, which would present in the normal skin at the edge of the biopsy scar. The recurrent melanocytic proliferation may best be viewed as a form of reactive hyperplasia, perhaps a response to growth factors from the healing wound, and not a direct recurrence of the preexisting nevus. It is possible that melanocytes in the region of the nevus have undergone some kind of “field change,” which makes the region of a nevus more susceptible to this phenomenon, since it is not seen in relation to scars from excisions or biopsies of other (nonmelanocytic) lesions. Complete excision is appropriate management for a lesion of this type (MPATH DX Category 2).
**1.3.2**

*Recurrent and Traumatized Nevi*

**Clinical Information**
This was sent in as an intradermal nevus from the breast.

**Reason for Consultation**
I favor an irritated compound nevus, moderately atypical (epidermal component)—I know that the breast is a “special site.” What do you think?

**Description**
These sections show a shave biopsy containing a dome-shaped nevoid melanocytic proliferation, 2 to 3 mm in diameter on the slide. It is comprised of predominantly nevoid melanocytes, showing evidence of maturation to a smaller cell type and dispersion into the reticular dermis at the base. A somewhat unusual feature is the presence of nested and a few single larger cells in the epidermis above the dermal component of the lesion, confined to the center of it. There is also fibroplasia in the dermis in this area. This type of epithelioid cell melanocytic hyperplasia can be seen in the epidermis above the dome-shaped or polypoid compound and dermal nevi and one may speculate that it might be due to prior trauma. In other words, this could be a phenomenon analogous to the “recurrent nevus phenomenon.” In summary, I would interpret this lesion as follows:

**Figure 1.3.2.1** A dome-shaped lesion comprised of orderly nevoid melanocytes that show evidence of maturation from superficial to deep, transected at the specimen base. There are some larger pigmented melanocytes in the epidermis and superficial dermis near the center of the lesion.
In this superficial region there is also fibroplasia of the papillary dermis, suggesting the possibility of trauma.

The atypical proliferation is confined to the center of the lesion and there is no “in situ” or atypical junctional component extending beyond the shoulder of the dermal component.

The cells in this region have large nuclei with pale chromatin and prominent nucleoli. The cytoplasm contains abundant pigment. The appearances are reminiscent of a “recurrent nevus”; however, there was no history of prior biopsy of this lesion.
I do not believe these changes approach criteria for melanoma in situ. One might consider the possibility of a dysplastic nevus; however, the changes are not present at the “shoulder” of the lesion. Because of this differential diagnosis, I would recommend evaluation of this patient’s other risk factors for melanoma; however, especially if there are no other clinically atypical nevi and/or a personal or family history of melanoma, I would expect these findings to have no particular significance. The atypical proliferation is completely excised; however, the benign background nevus extends to specimen margins and therefore possibly an additional excision procedure might be considered, or perhaps alerting the patient to report any evidence of recurrent pigment might suffice. The possibility of a special site nevus of the breast might also be considered; however, the usual pattern of large nested and dyshesive cells in large nests is not observed, and also these lesions do not typically present as dome-shaped compound or dermal nevi.

**OVERALL COMMENT**

Differential diagnosis could include a special site nevus of the breast; however, the appearances are not characteristic, as discussed above. Complete excision is appropriate management for this lesion (MPATH DX Category 2).
Recurrent Nevus Versus Melanoma

**Clinical Information**
This was sent in as a recurrent atypical nevus from the forehead of a 42-year-old man.

**Reason for Consultation**
This was sent in as a recurrent atypical nevus. I favor a recurrent compound nevus; there may be a little more suprabasal melanocytes than typically seen with recurrent “Pseudomelanoma.” I recommended reexcision. What do you think? Interestingly, this lesion was sent in 2 months ago as rule out BCC—I signed it out at the time as ulcerated AK consistent with traumatized solar keratosis. I reviewed the slides—very inflamed and hard to tell if some of the histiocytoid cells were nevus cells.

**Description**
These sections show a shave biopsy of skin that measures about 3 mm in diameter, with a few collections of orderly nevus cells transected at the base of the biopsy, overlain by an area of fibroplasia, consistent with the history of a prior shave biopsy at this site. In the epidermis, there is a moderately to highly cellular proliferation of nevoid to epithelioid melanocytes, containing moderate to abundant pigment in the form of relatively coarsely divided pigment granules. A few of the cells rise slightly above the junction, generally not beyond the middle third. There are a few nests of similar cells in the upper dermis; however, there is no evidence of tumorigenic or mitogenic activity in the dermis. Given the history that you describe, I would agree that these changes are consistent with recurrent nevus. It will be important to completely excise the lesion to rule out the possibility of recurrent melanoma extending beyond the borders of the dermal scar. This excision should therefore include a margin of normal skin around the scar of this procedure, and the scar of the previous procedure, as well as any residual lesion. Before rendering a final diagnosis, I would like to have the opportunity to review this reexcision, and also the prior biopsy.

**Figure 1.3.3.1** A superficial shave biopsy containing a moderately to highly cellular proliferation of melanocytes, with a somewhat asymmetrical profile.
1.3.3

**FIGURE 1.3.3.2** There is almost continuous basal proliferation of enlarged nevoid to epithelioid melanocytes. At the base of the lesion there are mature dermal nevic cells. The intervening stroma is fibrotic.

**FIGURE 1.3.3.5** There is moderate to severe atypia of the lesional cells in the form of nuclear enlargement and nucleoli; however, the chromatin is generally pale. Pagetoid scatter is confined to the lower third of the epidermis and is sparse.

**FIGURE 1.3.3.6**

**FIGURE 1.3.3.3**

**FIGURES 1.3.3.3 and 1.3.3.4** At each periphery, the lesion is reasonably well circumscribed. The proliferation of fibroplasia in the dermis extends to the specimen margin on each side.

**FIGURE 1.3.3.7**

**FIGURES 1.3.3.6 and 1.3.3.7** This lesion had been biopsied from the lesional site 2 months before and signed out as an ulcerated keratosis. There is an ulcer/excoriation, and it is impossible to appreciate the presence of any nevus cells in the specimen.
**DIAGNOSIS**

Skin, right forehead: Intraepidermal atypical melanocytic proliferation of uncertain significance, most consistent with a recurrent melanocytic nevus, and an associated dermal nevus with overlying fibrosis, transected at specimen margins, see Description and Comment.

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**COMMENT**

**COMMENT 1**

As noted above, I would like to have the opportunity to review the completely excised lesion and the prior biopsy before definitively determining that this atypical lesion is benign.

**COMMENT 2**

I have reviewed the prior biopsy, which as you mentioned in your note shows a very superficial biopsy of skin with an excoriating/ulcer, at the base of which there are a few vessels lined by plump endothelial cells, and a few ill-defined collections of somewhat similar looking cells, which could be nevic. Reassuringly, there is no severe atypia or mitotic activity of this dermal component, and there is no evidence whatsoever of any in situ component of a melanoma, tending to strongly support the diagnosis of recurrent nevus in the present specimen.

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**OVERALL COMMENT**

This lesion rather clearly represents a recurrent nevus even though there was no obvious nevus in the original biopsy. The presence of dermal nevus cells in the recurrent specimen from the same site nevertheless indicates that the nevus was in fact present. In this specimen, the fibrosis extends to the specimen margins. The atypical proliferation extends close to the margins and complete excision of it cannot be guaranteed. Therefore, consideration of an additional procedure with a clear margin of normal tissue is recommended (MPATH DX Category 2).
1.3.4

Recurrent Nevus Versus Melanoma

CLINICAL INFORMATION
Recurrent pigmentation at the site of prior biopsy of a nevus.

REASON FOR CONSULTATION
Previous biopsy is not available for review. I am concerned that this may be melanoma.

DESCRIPTION
These sections show a complex lesion characterized by an extensive dermal scar, with a history of prior biopsy of the nevus. In support of this history, there is residual nevus both deep to and on each side of the scar, representative of the dermal component of a congenital pattern nevus. A striking feature, of course, is in the epidermis above the scar where there is a moderately to highly cellular proliferation of relatively large nevoid to epithelioid melanocytes, which have rather abundant cytoplasm and prominent melanin pigment. The cells have moderately enlarged nuclei, with prominent nucleoli but without marked membrane irregularity or chromatin clumping. Similar cells are present in the papillary dermis, again with

FIGURE 1.3.4.1 A broad lesion characterized by extensive scarring in the dermis and moderately cellular proliferation of melanocytes in the epidermis. To the right side, there are remnants of dermal nevus.
1.3.4

**Figure 1.3.4.2** The left margin shows that the scar is surrounded by a minimal margin of normal dermis. A few atypical melanocytes are present in the epidermis confined to the region above the scar.

**Figure 1.3.4.3** The scar is also surrounded by normal dermis on the right margin. There are remnants of dermal nevus cells in the native dermis adjacent to the scar. Above the scar there is an atypical intraepidermal melanocytic proliferation.

**Figure 1.3.4.4** There are enlarged nevoid to epithelioid melanocytes with abundant pigment. There is moderate to severe nuclear atypia, although there is not marked hyperchromatism and pleomorphism. A few cells rise above the junction but there is no extensive pagetoid scatter.

**Figure 1.3.4.5** The remnant dermal nevus cells are mature and are located in the dermis adjacent to the scar.

Prominent nucleoli and without much evidence of maturation. There is no tumorigenic proliferation or mitotic activity in the dermis. A notable fact is that the atypical intraepidermal proliferation is confined to the epidermis above the scar and ceases at the edge of the scar in the section planes that are appropriately
1.3.4

oriented to demonstrate this feature. In other section planes, the scar extends close or to a lateral specimen margin. Taking these features together, the changes are essentially diagnostic of the phenomenon as “recurrent nevus,” which appears to be a form of reactive hyperplasia of melanocytes in regenerating epithelium above the scar of a prior biopsy of the nevus.

The key feature is the lack of extension beyond the scar. It is important to have the complete extent of the scar and background nevus available to rule out the possibility of persistent and recurrent melanoma, and it is also desirable to review the prior material. I will therefore interpret this material to some extent descriptively as follows:

**DIAGNOSIS**

Biopsy site reaction, with residual congenital pattern dermal nevus cells, and overlying atypical intraepidermal melanocytic proliferation, most consistent with the recurrent nevus phenomenon, with scar and residual nevus extending to lateral specimen margins, see Description and Comment.

**COMMENT**

This phenomenon was also described under the term “pseudomelanoma.” As noted above, it is important to rule out recurrent melanoma. I would therefore recommend an additional procedure to be sure this lesion has been completely removed with a margin of normal skin around the scar of this present procedure and any residual lesion. It would also be appropriate to review the prior material. If there is no evidence of melanoma in these procedures, then I believe that this is a completely benign phenomenon.

**OVERALL COMMENT**

Prior biopsy has not been made available for review in this case. Complete excision is appropriate management for this lesion (MPATH DX Category 2).
1.3.5

Recurrent and Traumatized Nevi

CLINICAL INFORMATION
53-year-old woman. 1 cm red scaly plaque-congenital nevus. Rule out atypia or other. Rule out Spitz. 4 mm punch.

REASON FOR CONSULTATION
The differential diagnosis could include a traumatized congenital nevus versus melanoma in situ arising in a congenital nevus. The process extends to the peripheral and deep margins of the specimen. In some sections dermal melanocytes are enlarged and some of them demonstrate deep pigmentation. The rest of the dermal component is nevoid with congenital features. There is no history of previous biopsy.

DESCRIPTION
These sections show a punch biopsy of skin showing complex changes including the presence of clusters of nevoid melanocytes in the dermis, extending into the reticular dermis in a pattern that is somewhat unusual but perhaps consistent with a “congenital pattern” nevus. In the superficial part of the biopsy, there is diffuse fibroplasia affecting the papillary dermis and superficial reticular dermis. This fibroplasia extends to both borders of the punch biopsy specimen and may correlate with the history of the patient “picking at” the lesion. In the overlying epidermis, there is an atypical intraepidermal proliferation of relatively small nevoid melanocytes, present as single cells and a few nests near the dermal–epidermal junction, with pagetoid scatter of similar cells into the epidermis, generally confined to the midspinous layer or lower. Cytologically, the cells tend to have relatively small although somewhat irregular nuclei, and mitotic figures are rare or absent. The cells in the dermis are similar to those in the epidermis, showing only slight if any evidence of maturation; however, the cellularity is low, and again mitotic figures are rare or absent. Reassuringly, a Ki-67 study is completely negative in

FIGURE 1.3.5.1 A partial biopsy of a broad and deep lesion, characterized by irregular distribution of lesional cells and reactive epithelial changes.
1.3.5

FIGURES 1.3.5.2 and 1.3.5.3 In the epidermis, there is quite prominent pagetoid scatter of lesional cells. Some cells in the dermis appear immature; however, there is no expansile proliferation of uniformly atypical cells.

FIGURE 1.3.5.4 There is complex fibroplasia in the superficial dermis, within which there are clusters of nevus cells.

FIGURE 1.3.5.5 Lesional cells, especially near the surface, demonstrate moderate to severe nuclear enlargement, irregularity, and hyperchromatism. There is no continuous basal proliferation, or high-level pagetoid scatter.

the dermal component and probably in the junctional component as well. Taking these findings together in conjunction with the history, I believe that these changes could be consistent with the so-called “recurrent nevus phenomenon,” although based on this material alone the possibility of a more significant process is difficult to rule out entirely. I would therefore interpret this lesion descriptively as follows:
I note that this lesion is described as a “1 cm red scaly plaque-congenital nevus,” which may explain some of its architectural features. As discussed above, I believe that the changes in the epidermis could be consistent with a traumatized nevus. If such is the case, then the atypical proliferation should be confined to the epidermis above the area of scarring. Ruling out a superficial melanoma will therefore require the complete excision of this lesion with borders of normal tissue, to evaluate this feature as well as other features such as size, circumscription, symmetry, and other features of this atypical proliferation.

**OVERALL COMMENT**

Given the clear history of recurrent trauma, it seems likely that the changes in this lesion are best described in terms of a variant of the recurrent nevus phenomenon. Complete excision is indicated to rule out other possibilities. It is important that any reexcision includes a clear margin of normal tissue, so as to rule out a true persistent lesion at the periphery of the scar. Complete excision is appropriate management for this lesion (MPATH DX Category 2). If the reexcision specimen were to show evidence of melanoma, then obviously additional therapy would be indicated.

**FIGURE 1.3.5.6** A Mart stain demonstrates the complex architecture of this lesion, presumably modified by superficial trauma.
Nevus Versus Melanoma

CLINICAL INFORMATION
Lesion of right upper arm in a 26-year-old woman.

REASON FOR CONSULTATION
I would appreciate your expert opinion on this melanocytic lesion from a 26-year-old female. Provisional interpretation: Atypical melanocytic proliferation; final diagnosis pending expert opinion.

FIGURE 1.3.6.1 A plaquelike superficial lesion with a central depression.

FIGURE 1.3.6.2 The lesion is comprised at its periphery of orderly nevus cells in the dermis with a few single cells and nests in the epidermis, mostly near the dermal–epidermal junction.

FIGURE 1.3.6.3 Cells in the dermis show evidence of maturation along nevic lines.
DESCRIPTION
These sections show an excision biopsy of skin, containing a moderately cellular proliferation of nevoid to epithelioid melanocytes, arranged in the epidermis predominantly in nests, with an admixture of single cells, a few of which rise slightly above the junction. There is an occasional mitosis in the junctional component, mostly if not exclusively within keratinocytes. In the dermis, there are nevoid melanocytes that show evidence of maturation from superficial to deep. Toward the center of the lesion, there is a region where the epidermal rete pattern is effaced and there is fibroplasia in the dermal component. The appearances in this region suggest the possibility of previous trauma. In any event, I do not believe these changes reach the level of significant concern for the possibility of melanoma and I would interpret this biopsy as follows:

DIAGNOSIS
Skin biopsy left upper arm: Compound nevus, with focal reactive changes most consistent with prior trauma, completely excised, see Description and Comment.
1.3.6

**COMMENT**

As noted above, there are some atypical architectural changes in this lesion that I believe are most likely related to trauma. There is no evidence of malignancy and the architectural features are not those of a dysplastic nevus. However, if this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, additional evaluation and possible surveillance might be indicated. This present lesion is completely excised.

**OVERALL COMMENT**

This lesion appears benign, and reexcision would not be mandatory even if it were present at specimen margins (MPATH DX Category 1 or 2).
2.0 High Chronic Solar Damage Superficial Atypical Melanocytic Proliferations

2.1 Lentigo Maligna Melanoma (High CSD Melanoma)
  2.1.1 Lentigo Maligna Melanoma and Possible Precursor Lesions
  2.1.2 Lentigo Maligna Melanoma With Desmoplastic Vertical Growth Phase Versus Atypical Neurotized Compound Nevus
  2.1.3 Intraepidermal Atypical Melanocytic Proliferation of Uncertain Significance, Regressing Melanoma Versus Benign Lichenoid Keratosis With Junctional Melanocytic Hyperplasia Versus Atypical Nevus
  2.1.4 Lentigo Maligna Melanoma, Invasive, Versus Incidental Dermal Nevus in Lentigo Maligna
  2.1.5 Nevoid Lentigo Maligna Versus Severely Dysplastic Nevus
  2.1.6 Nevoid Lentigo Maligna Versus Atypical Lentiginous Junctional Nevus
  2.1.7 Melanoma In Situ Versus Lentiginous Nevus With Atypia or Severe Dysplasia
  2.1.8 Melanoma In Situ Versus Severe Dysplasia

2.2 Actinic (Solar) Lentigo and Lentiginous Nevi in Sun-Damaged Skin
  2.2.1 Actinic Lentigo Versus Lentigo Maligna
  2.2.2 Actinic Lentigo Versus Lentigo Maligna
  2.2.3 Actinic Lentigo With Spindle Cells
  2.2.4 Atypical Lentigo Versus Regressing Melanoma
  2.2.5 Lentiginous Nevus Versus Lentiginous Melanoma
In the evolving etiologic/genetic/site related classification of melanocytic tumors (1), the presence of actinic elastosis is a critical histologic feature as a marker of chronic solar damage (CSD). Actinic elastosis is seen in almost all melanoma resection specimens. In melanomas of the superficial spreading type, the degree of elastosis tends to be mild to moderate, while in the high CSD lesions, elastosis is moderate to severe. In a grading scheme developed for classifying melanocytic tumors (2), mild actinic elastosis is defined as the presence of elastic fibers that can be barely visualized at 20X. Moderate actinic elastosis is characterized by elastic fibers that are visualized in bunches, while severe actinic elastosis is characterized by homogeneous clusters of gray material representing elastic fibers that have lost their fibrillary texture. Although there is overlap between the “low CSD” and the “high CSD” melanocytic tumors, this scheme does represent a useful approach to classifying variants of melanocytic tumors that differ from one another morphologically, and also in terms of their underlying genomic abnormalities.

The prototypic “high CSD” melanocytic tumor is lentigo maligna melanoma (LMM), which is discussed in the next section (2.1). In Section 2.2, benign pigmented lesions that occur in high CSD skin, predominantly actinic lentigines, are discussed. These lesions are commonly visualized in melanoma reexcision specimens. They are present in the low CSD melanomas as well, but are more common in a high CSD setting. In addition, of course, other attributes of chronic solar damage including actinic keratoses and squamous and basal cell carcinomas are seen in chronically sun-damaged skin.

The presence of CSD is useful in diagnostic histopathology. For example, a pagetoid proliferation of large epithelioid cells occurring in skin lacking CSD in a young person may represent a pagetoid Spitz nevus rather than a superficial spreading melanoma (SSM). Conversely, in skin with severe actinic elastosis, a lesion that presents some features of a dysplastic nevus is probably more likely to represent a nevoid lentigo maligna, a lesion simulating a dysplastic nevus, to be discussed in more detail in the next section.
LMM was clearly described as a subtype of melanoma by Clark in 1969 (3). At about the same time, a group of Australian pathologists led by McGovern had developed a similar classification (4). Recognizing the seminal contributions of Jonathan Hutchinson (5), the lesion termed LMM by Clark was termed “Hutchinson’s melanotic freckle” in this classification. This is a clinically derived term that was current in Australia then and continues to be used there.

**Etiologic, Genomic, and Site/CSD Classification for LMM**

LMM is the prototypic example of the “High CSD” form of melanoma. These lesions occur on chronically exposed skin, with evidence of severe solar damage both clinically and histologically. They occur in older age groups, and tend to occur in outdoor workers rather than the indoor workers who are intermittently exposed that constitute the majority of SSM patients. LMM typically does not have mutations of the BRAF oncogene and may be associated with mutations of NRAS and also of KIT (6).

**Clinical Features**

Clinically, these lesions usually demonstrate the “ABCD” criteria; however, early lesions may present as small, indefinite regions of hyperpigmentation. In contrast to SSM, their borders are impalpable and indefinite. When vertical growth phase supervenes, it typically presents as a nodular excrescence that may expand, become ulcerated, and bleed as with other melanomas. Desmoplastic vertical growth phase is more likely to occur with lentiginous melanomas in general, including LMM, compared to the superficial spreading subtype.

**Histopathology**

Histologically, in contrast to SSM, these lesions are not associated with epidermal hyperplasia and their borders are often not palpable until dermal invasion and tumorigenic proliferation have occurred. These lesions are characterized by low values for pagetoid scatter and nesting, a smaller nevoid to epithelioid cell type, and lesser degrees of pigmentation compared to SSM (1,7). Amelanotic melanomas are usually of the lentigo maligna subtype when in the radial growth phase, although nodular melanomas (i.e., tumorigenic vertical growth phase melanomas without an adjacent radial growth phase) may also on occasion be amelanotic. Some LMM may be moderately or even heavily pigmented.

The vertical growth phase in LMM may be comprised of epithelioid cells but is, perhaps more often than not, comprised of spindle cells. These are usually arranged in clusters of cells that are in contiguity with one another in an “epithelial” pattern. In some cases, the pattern is “desmoplastic,” where individual tumor cells are separated by delicate collagen fibers that have most likely been synthesized by the tumor cells themselves in a facultative fibroblastic pattern (8). These desmoplastic vertical growth phase tumors may also demonstrate schwannian...
differentiation, with wavy fiber bundles comprised of cells with serpentine nuclei. There also may be neurotropism, often in the form of cells involving the endoneurium and infiltrating among the axons, in contrast to the “perineural invasion” that characterizes most neurotropic cancers.

**Differential Diagnosis**

The differential diagnosis of LMM includes SSM. The significance of this distinction is relatively slight and the principal distinguishing features have been discussed above in the section on SSM. More importantly, lentigo maligna needs to be distinguished from various categories of atypical nevi, the most important of which perhaps are dysplastic nevi, discussed in the previous section.

In contrast to dysplastic nevi, the rete ridge pattern in LMM tends to be effaced while in dysplastic nevi the rete ridges are uniformly elongated. In some not uncommon cases the rete ridges are elongated (often only in part of the lesion), in a pattern termed “dysplastic nevus-like melanoma” (9). Other terms that have been applied to similar lesions are “lentiginous melanoma” (10) and “nevoid lentigo maligna” (11).

As a generalization, dysplastic nevus is a diagnosis that should be made with great caution in sun-damaged skin of an older subject. The melanocytic proliferation tends to be predominantly of single cells in LMM. There may be pagetoid scatter of these cells into the epidermis but this is less prominent than in SSM; however, any pagetoid scatter is of some assistance in distinguishing these lesions from atypical nevi. In addition to single cells, there may be a few nests in LMM. These nests tend to be haphazardly distributed across the lesion and they tend to be round rather than oval and to hang down from the interface in a pattern reminiscent of droplets of rain falling from a gutter. In contrast, nests in dysplastic nevi tend to bridge between adjacent elongated rete ridges. Dysplastic nevi also have concentric fibroplasia while LMM may have little or no fibroplasia, or if present the fibroplasia is diffuse. The lesional cells in the dermis in dysplastic nevi tend to be centrally placed with adjacent “shoulders.” In LMM, cells in the dermis tend to be haphazardly distributed across the lesion. Although not always present, the presence of any mitoses, whether junctional or dermal, can be diagnostically decisive as long as a benign or less significant condition (such as a pigmented spindle cell nevus or a pagetoid Spitz nevus) can be ruled out.

Another lesion that enters the differential diagnosis of LMM has been termed the “lentiginous nevus of the elderly.” This lesion was first described by Kossard in 1991 and there have been a few reports since (10–16). In a recent study of 14 cases, there were seven men and seven women. Clinically most of the lesions resembled atypical (dysplastic) nevi and they were all located on the back. Histologically, they had irregular lentiginous epidermal hyperplasia with the proliferation of individual melanocytes in the basal layer of the epidermis and absence of dermal nests. Focal upward migration of melanocytes into the epidermis was present in four of the cases. All of the lesions had cytologic atypia, generally in the moderate range. The Ki-67 proliferation was low, and mitotic activity was not described (16). The lentiginous nevus should be distinguished from lesions that have been termed “lentiginous melanoma.” These lesions occur in middle-aged and older patients and histologically present with a broad, lentiginous growth pattern of moderately atypical melanocytes showing focal nesting and pagetoid spread, without significant dermal fibroplasia or alteration of the rete ridges. This lesion shows significant overlap clinically and histologically with the atypical lentiginous nevus of the elderly (15).
Given the overlap of lentigo maligna and other melanomas with dysplastic nevi, and also with the lentiginous nevi of the elderly (16,17), it is not uncommon for there to be doubt as to whether a lesion meets sufficient criteria for a definitive diagnosis of melanoma. In such cases a descriptive diagnosis, such as “Intraepidermal melanocytic proliferation of uncertain significance” (IAMPUS) can be given if the lesion is entirely junctional, or “Superficial atypical melanocytic proliferation of uncertain significance” (SAMPUS), if there is a small dermal component that could represent invasive radial growth phase versus a small nevic component. In such a case, microstaging attributes that might apply if the lesion is interpreted as melanoma can be given as a guide to management planning.

**PRINCIPLES OF MANAGEMENT OF LMM**

The management of LMM is the same as that for other melanomas, although sometimes there is compromise of margins because of nearby vital structures such as an eye. Also, the borders are ill-defined both clinically and histologically, which can create problems with margin control. Most of these lesions when in situ will be managed as MPATH DX Category 3 and when invasive as Categories 4 or 5.

**References**

2.1.1

Lentigo Maligna Melanoma and Possible Precursor Lesions

**CLINICAL INFORMATION**
Three separate biopsies from left posterior shoulder of an 85-year-old female over a period of 3 years. The biopsies were performed in 4 years and 1 year ago, and recently.

**REASON FOR CONSULTATION**
The original biopsy revealed a junctional Clark's (mildly dysplastic) melanocytic nevus (see enclosed report). In that report it was mentioned that there was mild melanocytic atypia, and that the peripheral and deep margins of the specimen were negative in the plane of sectioning.

The next biopsy at presumably the same anatomic location was signed out as an atypical melanocytic proliferation consistent with a persistent/recurrent Clark's (dysplastic) nevus, involving the peripheral edge of the biopsy. It was mentioned that the differential diagnosis included early melanoma in situ evolving within a preexisting nevus, and a reexcision was recommended.

The most recent specimen, in my opinion, has histologic features concerning for melanoma because of the architectural symmetry, ill-defined borders, contiguous proliferation of atypical solitary melanocytes, and some pagetoid spread of melanocytes within the epidermis. I do not see definitive features of a scar consistent with a prior biopsy site. I believe that an additional procedure is warranted to ensure that the lesion has been completely removed.

**DESCRIPTION**
These sections show, in the original biopsy, a shave biopsy of a lesion characterized by single and nested melanocytes arranged mainly near the dermal–epidermal junction, in chronically sun-damaged skin. In some areas there are nests that bridge between adjacent elongated rete ridges. In other areas, there are a few nests that hang down from the interface in a dropletlike pattern. The lesion is rather poorly circumscribed, with single cells in the epidermis at its periphery. A few cells rise slightly above the junction; however, there is no extensive pagetoid scatter. Cytologic atypia is mild to moderate but relatively uniform. This lesion is difficult to interpret. Although cytologic atypia is mild to moderate rather than severe, there are somewhat concerning architectural changes, and one is somewhat more concerned about

![Image](image_url)

**FIGURE 2.1.1.1** A broad, sparsely cellular lesion in sun-damaged skin.
FIGURE 2.1.1.2 There are patchy lymphocytes and melanophages in the dermis and a few melanocytes in the epidermis.

FIGURE 2.1.1.3 There is an increased number of nevoid melanocytes present as a few nests and as single cells near the dermal–epidermal junction and also demonstrating pagetoid scatter into the epidermis generally not beyond the middle third. Well-organized features of a dysplastic nevus, such as bridging nests and concentric fibroplasia, are not observed. Appropriate diagnoses for this lesion could be “Intraepidermal atypical melanocytic proliferation of uncertain significance (“IAMPUS”), or perhaps ‘Atypical lentiginous junctional proliferation.’” Changes probably fall short of the diagnosis of “nevus lentigo maligna,” although this would be a reasonable consideration.

FIGURE 2.1.1.4 This shave biopsy represents a recurrence of the above lesion at the same site and shows, similar to the previous specimen, a broad, sparsely cellular lesion in sun-damaged skin.

a lesion in chronically sun-damaged skin of older subjects. I would agree with the concern that you expressed about this lesion for these reasons in your original report, namely that this is an atypical lesion occurring in sun-damaged skin. I would interpret it descriptively as follows.

Sections of the first recurrence show a shave biopsy of similar sun-damaged skin, containing a somewhat more cellular proliferation of nevoid and nevoid to epithelioid melanocytes, focally exhibiting severe and uniform cytologic atypia. Some of these cells are confined to the epidermis above the scar,
while others appear to extend some distance beyond the periphery of the scar. This latter feature raises concern for evolving melanoma in situ extending beyond the scar. In large measure, however, this concern is based on retrospective knowledge of the subsequent recurrence. I would therefore interpret this lesion descriptively as follows below.

Sections of the latest recurrence show a quite broad, moderately to focally more highly cellular proliferation of rather uniformly atypical relatively large epithelioid melanocytes, arranged singly and in nests, the latter being irregularly distributed and varying somewhat in size, shape, and orientation, along the dermal–epidermal junction. The lesion
CASE 1: LENTIGO MALIGNA MELANOMA AND POSSIBLE PRECURSOR LESIONS

2.1.1

**FIGURE 2.1.1.8** In addition to fibroplasia and solar damage in the dermis, there is a moderately cellular proliferation of atypical melanocytes in the epidermis, and there are irregularly clustered collections of atypical melanocytes in the dermis.

**FIGURE 2.1.1.9** Atypical melanocytes in the epidermis are present as single cells and as small nests that “hang down” from the interface.

**FIGURE 2.1.1.10** Higher magnification demonstrates clusters of atypical cells in the dermis in relation to diffuse fibroplasia and moderate to severe chronic solar damage.

**FIGURE 2.1.1.11** A Melan-A stain demonstrates continuous basal proliferation to a somewhat greater extent than was appreciated in the hematoxylin and eosin sections. Cells in the dermis are also highlighted.

is very broad, extending 8 mm or more in diameter across the shave biopsy specimen. Cells similar to those in the epidermis are present in the papillary dermis as small nests of cells, which are not clearly larger than the largest nests in the epidermis. I would regard these as representing invasive melanoma because they cytologically resemble the cells in the epidermis. Although the prior biopsy sites
2.1.1

are not clearly recognizable, there is fibroplasia in the papillary dermis and these biopsy sites were very small. In summary, I would interpret this material as follows:

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin, left posterior shoulder, shave biopsy: Intraepidermal atypical melanocytic proliferation (IAMPUS), see Description and Comment.</td>
</tr>
<tr>
<td>Skin, left posterior shoulder, shave biopsy (first recurrence): IAMPUS, extending to specimen margins, see Description and Comment.</td>
</tr>
<tr>
<td>Skin, left posterior shoulder (second recurrence): Malignant melanoma, lentigo maligna type, with nontumorigenic and nonmitogenic invasive radial growth phase, nonulcerated, Clark’s level II, greatest Breslow thickness 0.37 mm, see Description and Comment.</td>
</tr>
</tbody>
</table>

**COMMENT**

I would agree with your recommendation for careful follow-up of the original lesion. One might also have considered an additional excision procedure; however, there is certainly not, to my mind, sufficient evidence to call this lesion an established melanoma, and follow-up would certainly be a reasonable option. In retrospect at least, the possibility that this lesion represents a so-called “nevoid lentigo maligna” should be seriously considered. In the second lesion, there is an atypical proliferation above the scar and, possibly, extending beyond the periphery of the scar in some of the deeper levels. In the latest specimen, there is clear evidence of a melanoma said to have arisen at the same site. Although a definitive scar is not clearly identified, there are changes consistent with prior biopsy sites. In the absence of fully established tumorigenic and mitogenic vertical growth phase, the prognosis for this lesion should be excellent provided that local control can be achieved. Changes of in situ melanoma extend at least within a fraction of a millimeter of a lateral specimen border of this very broad lesion. The Melan-A study supports the diagnosis by demonstrating continuous and pagetoid proliferation in the junctional component.

**OVERALL COMMENT**

The diagnosis of a dysplastic nevus should be made with great caution in chronically sun-damaged skin of elderly subjects. Most lesions that demonstrate dysplastic nevuslike features in this situation represent either fully evolved nevoid lentigo maligna, or ill-defined atypical lentiginous melanocytic proliferations that may represent precursor lesions or early evolving in situ melanomas. Management of these lesions is typically by complete excision—MPATH DX Category 2, or perhaps 3. The recurrent melanoma represents a T1a melanoma and would be managed by complete excision with approximately 1 cm margin—MPATH DX Category 4.
2.1.2

Lentigo Maligna Melanoma With Desmoplastic Vertical Growth Phase Versus Atypical Neurotized Compound Nevus

**CLINICAL INFORMATION**

Lesion of right shoulder, r/o melanoma versus nevus.

**REASON FOR CONSULTATION**

Is this anything other than a moderately atypical neurotized compound nevus?

**DESCRIPTION**

These sections show a shave biopsy of skin, containing a poorly circumscribed asymmetrical, subtle, and focally more cellular proliferation of nevoid to epithelioid melanocytes along the dermal–epidermal junction in skin demonstrating severe actinic elastosis.

**FIGURE 2.1.2.1** A relatively broad lesion with irregular thickening and thinning of rete ridges and a sparsely cellular infiltrate in the dermis.

**FIGURE 2.1.2.2** At the periphery there are pigmented melanophages in the dermis and an increased number of melanocytes in the epidermis, many of them suprabasal.

**FIGURE 2.1.2.3** Atypical intraepidermal melanocytic proliferation in a region of elongated rete ridges. Appearances resemble dysplastic nevus; however, single cells predominate over nests and there is pagetoid scatter although not beyond the middle third.
2.1.2

**FIGURE 2.1.2.4** Near the center of the lesion there is a region of increased cellularity of the papillary dermis.

**FIGURE 2.1.2.5** Cells in the papillary dermis are delicate spindle cells and there is a sprinkling of lymphocytes.

**FIGURE 2.1.2.6**

**FIGURES 2.1.2.6 and 2.1.2.7** S100 stain highlights the increased cellularity in the epidermis and also labels the spindle cells in the papillary dermis.

These findings are quite concerning for melanoma in situ of the lentigo maligna type with features of so-called “nevroid lentigo maligna.” Rather eccentrically placed within the lesion, there is a dermal component comprised of spindle cells, with somewhat serpentine nuclei, extending into the upper reticular dermis in a rather infiltrative pattern although to a depth of only approximately 0.5 mm. I am concerned that this component may represent a superficial desmoplastic vertical growth phase that, while minimal, could, of course, have potential for recurrence and progression if not completely removed at this time. I will therefore order a Melan-A stain to better evaluate the junctional component and an S100 stain to better define the extent of the dermal component. For the present I would interpret this lesion descriptively as follows:
CASE 2: LENTIGO MALIGNA MELANOMA VERSUS ATYPICAL NEUROTIZED COMPOUND NEVUS

2.1.2

**PROVISIONAL DIAGNOSIS**

Right superior shoulder: Atypical intraepidermal and dermal melanocytic proliferation, concerning for the possibility of nevoid lentigo maligna with a superficial desmoplastic vertical growth phase, see Description and Comment.

**COMMENT 1**

As noted above, S100 and Melan-A stains are pending and will be reported later.

**COMMENT 2 (A FEW DAYS LATER)**

The immunostains have been reviewed. The S100 and Melan-A stains both highlight extensive continuous basal and patchy pagetoid proliferation of melanocytes in the epidermis, consistent with melanoma in situ. The S100 highlights the atypical spindle cells in the dermis, which are associated with a desmoplastic stromal response. These cells are negative with Melan-A, as expected in desmoplastic melanoma, supporting the diagnosis, which is therefore revised as follows:

**FIGURES 2.1.2.8 and 2.1.2.9**

Melan-A stain highlights the junctional component, but the dermal spindle cells are negative.
2.1.2

**FINAL DIAGNOSIS**

Skin, right superior shoulder: Malignant melanoma, lentigo maligna type, nonulcerated, with pure desmoplastic vertical growth phase, Clark level IV, Breslow thickness not less than 0.64 mm, extending close to the specimen base, see Comment.

**COMMENT**

The dermal mitotic rate is zero, tumor-infiltrating lymphocytes are absent, there is no regression, there is no ulcer, there are no satellites and there is no vascular, lymphocytic, or neural invasion evident in this material. Changes extend close to the base and to a peripheral margin of the specimen.

**OVERALL COMMENT**

It is unusual to see a small desmoplastic melanoma at this early stage of its evolution. While it is by no means certain that this lesion would have progressed to a more advanced stage, it is clearly a lesion that should be excised locally in order to prevent any possibility of persistence, recurrence, or future progression of it. Based on the microstaging attributes noted above, the prognosis for this lesion should be excellent. The prognosis for “pure” desmoplastic melanoma is if anything better than that for melanomas of similar thickness. This lesion could probably be managed with a relatively generous wide local excision—MPATH DX Category 4.
Intraepidermal Atypical Melanocytic Proliferation of Uncertain Significance, Regressing Melanoma Versus Benign Lichenoid Keratosis With Junctional Melanocytic Hyperplasia Versus Atypical Nevus

CLINICAL INFORMATION
Atypical lesion of the right arm in a 68-year-old man.

REASON FOR CONSULTATION
Our differential: Benign lichenoid keratosis with junctional melanocytic hyperplasia, rule out melanoma in situ.

DESCRIPTION
These sections show a shave biopsy of skin, containing a lesion characterized, at scanning magnification, by a brisk bandlike lymphocytic infiltrate in the dermis, associated with severe actinic elastosis. The overlying epidermis shows, for the most part, little change of the stratum corneum, with focal compact hyperkeratosis, and a prominent granular layer. The lymphocytic infiltrate in some areas is lichenoid and especially in these areas there are clusters of cells with pigment consistent with melanocytes. The presence of these cells is confirmed in an MITF stain. However, there is no extensive continuous basal proliferation and only slight focal pagetoid scatter of these cells into the epidermis, without severe uniform atypia or mitotic activity, falling short of criteria for melanoma in situ. There is also keratinocytic atypia, and the differential diagnosis for this lesion could include a lichenoid actinic keratosis, a benign lichenoid keratosis, or a regressing melanoma in situ. I cannot rule out the latter possibility and would therefore interpret this lesion descriptively as follows:

FIGURE 2.1.3.1 A broad lesion with an irregular distribution of lymphocytes in the dermis and with severe actinic elastosis. In the epidermis, there are single and some nested melanocytes with some nests bridging between adjacent elongated rete ridges.
2.1.3

**FIGURE 2.1.3.2** There is a nest of melanocytes bridging between adjacent rete ridges but in general, the epidermal rete ridge pattern is effaced. There is a region where there is fibroplasia and lymphocytes in the papillary dermis but no lesional cells in the overlying epidermis or in the dermis, consistent with a focus of regression of the type seen in radial growth phase melanomas (radial growth phase regression).

**FIGURE 2.1.3.3** Irregular nesting and pagetoid scatter of nevoid to epithelioid melanocytes demonstrating only mild to moderate cytologic atypia.

**FIGURE 2.1.3.4** Another region illustrating irregular proliferation of single and nested melanocytes.

**FIGURE 2.1.3.5** In this region there are elongated rete ridges with bridging of nests. Some basal keratinocytes are enlarged with nucleoli; however, there is no severe atypia and also there is no parakeratosis.
COMMENT

As noted above, I cannot rule out regressing melanoma in situ, although the differential diagnosis could include reactive atypia in association with a lichenoid infiltrate. Because these changes extend close to specimen margins, I would recommend an additional procedure to be sure this lesion has been removed with a margin of normal skin, and follow-up for the patient because of his severe actinic skin damage associated with melanocytic and keratinocytic atypia.

OVERALL COMMENT

In these present images, I would favor a diagnosis of melanoma in situ. Nevertheless, the lesion lacks high-grade atypia, and continuous basal proliferation or pagetoid proliferation are not prominent features. Complete excision of this lesion should be curative (MPATH DX Category 3), and because of the presence of an atypical melanocytic proliferation in sun-damaged skin, consideration of skin surveillance would also be reasonable.

FIGURES 2.1.3.6 and 2.1.3.7 MITF stain demonstrates scattered positive cells along the junction, consistent with the presence of an atypical melanocytic proliferation. As a cautionary note, MITF can stain macrophage nuclei, but these cells are clearly melanocytic as judged by their location.

DIAGNOSIS

Skin, right arm: Intraepidermal atypical melanocytic proliferation (IAMPUS), regressing melanoma in situ cannot entirely be ruled out, see Description and Comment.
2.1.4

Lentigo Maligna Melanoma, Invasive, Versus Incidental Dermal Nevus in Lentigo Maligna

**CLINICAL INFORMATION**

Atypical lesion of the left shin in an 85-year-old woman.

**REASON FOR CONSULTATION**

I favor melanoma, level II-III, at least 0.35 mm. What do you think?

**DESCRIPTION**

These sections show a broad shave biopsy of skin showing severe actinic elastosis and containing a moderately to highly cellular proliferation of nevoid to epithelioid melanocytes arranged as single cells and nests with single cells predominating along the dermal-epidermal junction. There are foci where cells protrude into the papillary dermis and into the upper dermis.

*Figure 2.1.4.1* A broad lesion with an asymmetrical distribution of cellularity in the epidermis and in the dermis.

*Figure 2.1.4.2* There is severe actinic elastosis in the dermis, and in the epidermis there are irregularly spaced nests and single cells.
case 4: lentigo maligna melanoma, invasive, vs incidental dermal nevus in lentigo maligna

2.1.4

FIGURE 2.1.4.3 There is an area of expansion of the papillary dermis by clusters of cells similar to those in the epidermis.

FIGURE 2.1.4.4 The cells are uniformly albeit moderately atypical and are arranged in nests that are piled up upon one another in an “accretive” growth pattern.

FIGURE 2.1.4.5 In another area, small clusters of cells similar to those in the epidermis are present in the superficial dermis; while to the bottom right there are smaller cells.

FIGURE 2.1.4.6 The smaller cells have a characteristic of nevus cells representing a remnant of an associated dermal nevus. This may represent a precursor nevus or, perhaps more likely, a nevus that has been overrun by the melanoma.
2.1.4

reticular dermis. In one of these foci the cell type is more epithelioid, resembling those in the overlying epidermis, and there is little evidence of maturation. In another focus, there is evidence of maturation along nevic lines, and I would tend to favor that these cells represent remnants of a dermal nevus overgrown by the in situ melanoma. In any event, there is no mitotic activity or expansile tumorigenic proliferation in the dermis, and in summary I would agree with your interpretation of this lesion as follows:

**DIAGNOSIS**

Skin, left shin: Malignant melanoma, lentigo maligna type, nonulcerated with nontumorigenic nonmitogenic invasive radial growth phase, Clark's level II, greatest Breslow thickness 0.36 mm, present at specimen base and margins, see Description and Comment.

**COMMENT**

The dermal mitotic rate in this lesion is zero, tumor-infiltrating lymphocytes are essentially absent, there is fibroplasia with absence of cells in the dermis and overlying epidermis consistent with radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. I have interpreted a slightly deeper cluster of cells as remnants of an associated nevus. If these were interpreted as nevoid invasive melanoma, the diagnosis would be the same except that the thickness would be not less than 0.55 mm, with lesional cells present at the base of the biopsy. Based on either interpretation the prognosis for this lesion should be excellent following complete local excision.

**OVERALL COMMENT**

The distinction between nevoid maturation of melanoma cells and a preexisting dermal nevus can be difficult to make. If there is continuity of the cells in question with unquestioned melanoma cells in the overlying epidermis, the diagnosis is relatively simple. If this is not the case, then one must rely on cytologic atypia and the presence or absence of mitotic figures. However, most examples of differentiated nevoid vertical growth phase are lacking in mitotic activity. While this distinction can be important in terms of microstaging the melanoma, these “well-differentiated” thin and small vertical growth phase lesions are not likely to be associated with competence for metastasis. This lesion should most likely be treated by complete excision with a margin of approximately 1 cm (MPATH DX Category 4).
2.1.5

Nevoid Lentigo Maligna Versus Severely Dysplastic Nevus

CLINICAL INFORMATION
Lesion of the left neck in a 54-year-old man.

REASON FOR CONSULTATION
Is this anything other than a moderately to severely atypical junctional nevus?

DESCRIPTION
These sections show a moderately to focally more highly cellular poorly circumscribed junctional melanocytic proliferation that measures about 4 mm in diameter on the slide and is located in skin with severe actinic elastosis. At the periphery of the lesion,

FIGURE 2.1.5.1 A broad, asymmetric moderately to highly cellular proliferation in skin with severe chronic solar damage.

FIGURE 2.1.5.2 There are nests that are unevenly spaced across the junction, and tend to hang down from the interface in a dropletlike pattern.

FIGURE 2.1.5.3 There are also single cells along the dermal–epidermal junction.
it is poorly circumscribed, with single cells near the dermal–epidermal junction. Toward the center of the lesion, there are some nests that hang down from the interface in a dropletlike pattern, and closer to the center there is a proliferation of much larger epithelioid cells, forming nests that tend to become confluent. Among these cells, there are scattered mitoses. Based on the poor circumscription of the lesion, the lack of better developed architectural features of a dysplastic nevus, the uniform atypia and mitotic activity in the junctional component, as well as the presence of a few suprabasal lesional cells and involvement of a skin appendage extending to the specimen base, I would regard this lesion as a melanoma albeit with nevoid features and would characterize it as follows:

FIGURE 2.1.5.4 At least a single lesional junctional mitosis is identified.

FIGURE 2.1.5.5

FIGURES 2.1.5.5 and 2.1.5.6 In this region there is severe uniform atypia of epithelioid melanocytes with fibroplasia and a more prominent lymphocytic infiltrate in the dermis.
COMMENT

In the absence of invasion of the dermis or any other nonepithelial structures, the prognosis for this lesion is obviously excellent. There is no radial growth phase regression and no ulcer. Although the lesion has nevoid features there is no clear evidence of an associated nevus. As already noted, changes extend close or to specimen margins and I would, of course, recommend a definitive excision procedure and appropriate follow-up for this patient.

OVERALL COMMENT

Another example of the difficulty in distinguishing between dysplastic nevus and nevoid lentigo maligna, however, the latter diagnosis is much more likely in chronically sun-damaged skin as in this case. This lesion is appropriately managed by reexcision with approximately 5 mm margins (MPATH DX Category 3).
2.1.6

Nevoid Lentigo Maligna Versus Atypical Lentiginous Junctional Nevus

**Clinical Information**
An irregular variegated pigmented macule on the cheek of a 61-year-old man.

**Reason for Consultation**
I favor a severely atypical compound (predominantly junctional) nevus. What do you think?

**Description**
These sections show a shave biopsy of skin containing a moderately to highly cellular proliferation of nevoid to epithelioid melanocytes, present in the epidermis with single cells predominating in some areas associated with effacement of rete ridges, and present in a continuous basal pattern. In other areas there are nests with a suggestion of bridging nests; however, on balance I believe this lesion is best interpreted as LMM with, perhaps, features of so-called “nevoid lentigo maligna” or “dysplastic nevus-like melanoma.” Focally, in a region of diffuse fibroplasia in the papillary dermis, there is a nest that appears to be separate from the overlying epidermis, which I would characterize as representing superficial invasion and in summary I would interpret this lesion as follows:

*Figure 2.1.6.1* A broad, superficial lesion with variably effaced and exaggerated epidermal rete ridge patterns.

*Figure 2.1.6.2* *Figure 2.1.6.3* *Figures 2.1.6.2 and 2.1.6.3* There is an increased number of single melanocytes and ill-defined nests in a patchy but focally continuous pattern along the dermal–epidermal junction. In the dermis, there is moderate to severe actinic elastosis.
FIGURES 2.1.6.4 and 2.1.6.5 In another region there are elongated rete ridges with nests of atypical melanocytes mainly near their tips and sides, some bridging between adjacent rete. There is moderate to severe relatively uniform cytologic atypia. In the dermis there is concentric fibroplasia and there is a patchy lymphocytic infiltrate. These changes overlap with those of a dysplastic nevus.

FIGURE 2.1.6.6 There is a nest of cells similar to those in the epidermis present in the dermis in relation to an area of diffuse fibroplasia, consistent with focal nontumorigenic nonmitogenic invasive melanoma.
COMMENT

The dermal mitotic rate is zero, tumor-infiltrating lymphocytes are essentially absent, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is no associated nevus and actinic elastosis in the dermis is moderate. Changes of in situ melanoma stand to lateral specimen margins. This lesion should be treated by excision with up to a 1 cm margin, depending on the exact location and surgical considerations (MPATH DX Category 4).

OVERALL COMMENT

The differential diagnosis for this lesion could include severely dysplastic nevus or a “lentiginous junctional nevus of the elderly,” with atypia. I favor a melanoma because of the considerable breadth of the lesion, the single-celled basal proliferation, the diffuse fibroplasia in the papillary dermis, and the moderate to severe cytologic atypia, all of which are features more characteristic of melanoma than of a nevus.
2.1.7

Melanoma In Situ Versus Lentiginous Nevus With Atypia or Severe Dysplasia

Clinical Information
A 57-year-old man with a history of melanoma in situ and a reexcision specimen.

Reason for Consultation
Enclosed are two slides for your review. The original biopsy was read at an outside institution as “melanoma in situ involving the peripheral specimen margins.” The reexcision was read at an outside institution as “malignant melanoma in situ, residual, and scar, extending to one lateral margin.” Our interpretation on the slides is that there is no residual melanocytic proliferation identified. The dermatologist told us that there is no residual pigment lesion observed.

Description
Sections of the first biopsy slide show a very broad, superficial shave biopsy of sun-damaged skin, containing a moderately cellular proliferation of nevoid to epithelioid melanocytes, arranged in nests that tend to be unevenly distributed along the dermal–epidermal junction. Although there are some bridging nests, there are also nests that hang down from

Figure 2.1.7.1 A very broad shave biopsy containing a very broad, moderately to highly cellular melanocytic proliferation in the epidermis.
FIGURES 2.1.7.2–2.1.7.6 The lesion is comprised of nests that are irregularly distributed along the interface in chronically sun-damaged skin. Some nests hang down from the interface in a dropletlike pattern. There is relatively uniform cytologic atypia albeit mild to moderate in degree. In the dermis there is severe actinic elastosis.

FIGURE 2.1.7.7 A broad, wide, and deep reexcision specimen. There is a central biopsy site reaction.
FIGURES 2.1.7.8 and 2.1.7.9 There is a clear margin of normal (albeit elastotic) skin between the periphery of the biopsy site reaction and the inked specimen margin.

FIGURE 2.1.7.10 At high magnification at the periphery of the scar, there are reactive changes with lymphocytes and histiocytes. There may perhaps be rare melanocytes; however, there is no continuous proliferation of uniformly atypical cells, and no severe uniform atypia, no mitotic activity, and in short, no evidence of residual melanoma. At the left of the pictures there are a few slightly enlarged basal melanocytes consistent with so-called “actinic atypia” as may be seen in chronically sun-damaged skin.
2.1.7 the interface, and focal areas where there is predominance of single cells, with a few single cells rising above the junction. In the context of a very broad lesion in chronically sun-damaged skin, I would agree that these changes are best interpreted as melanoma in situ, with some features overlapping with melanocytic dysplasia consistent with so-called “nevoid lentigo maligna,” which I would characterize as follows below.

Sections of the reexcision specimen show a biopsy site reaction centrally placed in a wide and deep reexcision specimen. There is severe actinic elastosis. In the overlying epidermis there is a slightly increased number of melanocytes, some which have slightly enlarged nuclei; however, there is no severe uniform atypia, no continuous basal proliferation, no pagetoid scatter, and in short no evidence of residual melanoma either at the periphery of the biopsy site or elsewhere.

**DIAGNOSIS**

| Skin, left extensor arm (shave biopsy): Melanoma in situ, lentigo maligna type, with nevoid features (nevoid lentigo maligna) extending to lateral specimen margins. |
| Skin, left extensor arm (wide reexcision specimen): Biopsy site reaction, with no residual melanoma, and with severe actinic elastosis and mild melanocytic hyperplasia with slight actinic atypia. |

**COMMENT**

In the biopsy specimen, there is no invasion of the dermis and no evidence of radial growth phase regression. The lesion is nevoid; however, there is no clear evidence of an associated nevus. The differential diagnosis could perhaps include a “lentiginous nevus of the elderly”; however, the great breadth of the lesion, the irregular distribution of the nests, and the presence of an admixture of single cells with some pagetoid scatter favor a “high CSD” melanoma, in my opinion. There are some nevoid or nevuslike features consistent with descriptions of nevoid lentigo maligna, dysplastic nevuslike melanoma, and lentiginous melanoma. Such a lesion should be completely excised with an appropriate margin, for example, 5 mm (MATH DX Category 3).

**OVERALL COMMENT**

In the interpretation of reexcision specimens, it is important to realize that residual melanoma is likely to be present at one or another periphery of the biopsy site reaction, or at the deep part of the biopsy site reaction in the case of residual invasive melanoma or residual melanoma involving skin appendages. Atypical melanocytes elsewhere in the specimen may represent an independent lesion. Usually, these represent so-called “actinic atypia,” which may be diffuse within the specimen, or actinic lentigines with atypia. It is important not to overinterpret these changes as melanoma, especially if they involve the specimen margin. Changes in the epidermis above a biopsy site reaction should also be interpreted with caution as it is quite likely that they represent a reactive atypical hyperplasia of melanocytes, akin to the “recurrent nevus phenomenon” (see Section 1.3).
2.1.8

Melanoma In Situ Versus Severe Dysplasia

**Clinical Information**
Pigmented lesion of the right midback in a 58-year-old man.

**Reason for Consultation**
I favor a severely atypical compound (predominantly junctional) nevus with epidermal confluence—bordering on melanoma in situ—what do you think?

**Description**
These sections show a shave biopsy of skin, containing a moderately to highly cellular proliferation of nevoid to small epithelioid melanocytes, arranged in nests along the dermal–epidermal junction. Especially at the periphery of the lesion there are many nests bridging between adjacent elongated rete ridges and there is concentric eosinophilic and lamellar fibroplasia. Toward the center of the lesion, the nests tend to become somewhat confluent and there are single cells, some of which extend up into the epidermis in a pattern of pagetoid scatter although generally not beyond the lower third. Cytologically, there is mild to moderate atypia predominantly involving randomly scattered lesional cells. A few similar cells appear to be in the dermis. We will order a Melan-A stain to evaluate this and also the degree of confluence and scatter of the junctional component. For the present I will interpret this lesion descriptively as follows:

![Figure 2.1.8.1](image) A relatively broad, superficial lesion with generally uniform epidermal contours and somewhat asymmetrically distributed lymphocytic infiltrate in the dermis.
2.1.8

**FIGURE 2.1.8.2** At one border the proliferation is predominantly nested. There is mild to moderate actinic elastosis in the dermis.

**FIGURE 2.1.8.3** In other areas there is a tendency to thickening and/or effacement of the rete and to an increased number of single cells extending into the epidermis in a pagetoid scatter pattern generally not beyond the middle third of the epidermis.

**FIGURE 2.1.8.4** Pagetoid scatter into at least the middle third of the epidermis.

**FIGURE 2.1.8.5** In the dermis there is concentric fibroplasia and a patchy lymphocytic infiltrate.
COMMENT

COMMENT 1

The diagnosis of severe dysplasia is based on a combination of “severe” architectural disorder and “moderate” cytologic atypia in this case. This lesion is occurring in skin with mild but definite actinic elastosis in a middle-aged male patient, somewhat increasing the probability that the changes described indeed represent evolving melanoma. We will order Melan-A stain to better evaluate the architecture of the lesion. Changes in the epidermis extend close to specimen margins. I would recommend an additional procedure to be sure this lesion has been completely removed. Based on the severe dysplasia, I would also recommend consideration of periodic follow-up of this patient’s skin, especially if he has other clinically atypical nevi and/or a family or personal history of melanoma.

COMMENT 2 (A FEW DAYS LATER)

The Melan-A study shows pagetoid scatter of lesional cells generally not beyond the lower third. There are a few more cells in the dermis than are readily recognized in the H&E sections; however, these seem to be small and mature and consistent with dermal nevus cells. In any event, there is no tumorigenic or mitogenic dermal component. These findings tend to support the diagnosis of evolving melanoma in situ and I would recommend definitive management and follow-up based on this diagnosis.
Melan-A staining can tend to overemphasize continuous patterns of staining and should be interpreted with caution and/or can be combined with an MITF or Sox 10 nuclear stain. This lesion presents overlapping features of SSM, nevoid lentigo maligna melanoma, severe melanocytic dysplasia, and “lentiginous nevus of the elderly,” and might well have been interpreted descriptively as “IAMPUS.” Given the diagnosis of “consistent with evolving melanoma in situ,” complete excision would be appropriate management (MPATH DX Category 2 or 3).
Once known as “senile lentigo” or “lentigo senilis” (1), actinic lentigines are almost ubiquitous lesions in CSD skin. Multiple solar lentigines or “sunburn freckles,” commonly seen on the upper back and shoulders of adults, are typically considered as a sign of prior sun exposure and have been associated quantitatively with past severe sunburn episodes (2). Lentigines are characterized by concurrent proliferation and/or activation of melanocytes and keratinocytes, so that it can be debated whether they are primarily keratinocytic or melanocytic lesions (3,4).

The histologic appearances are characterized by some combination of three attributes: hyperpigmentation of basal keratinocytes, elongation of rete ridges, and prominence of melanocytes (5). One or perhaps even more of these attributes can be lacking. Thus, one may see a small region of hyperpigmentation of basal keratinocytes in isolation, or in conjunction with the elongated rete ridges, without an observable increase in melanocytes. Nevertheless, careful quantitative studies have demonstrated that melanocytes are increased in actinic lentigines (6). This is the reason for the use of the term “lentigo.” A lentigo, compared to a freckle or ephelid, is a lesion that is characterized by an increased number of melanocytes in addition to hyperpigmentation of the basal epidermis. These lesions, called lentigines by histopathologists and by dermatologists, are more often called freckles by members of the public and also, probably, by epidemiologists. Studies that have compared the frequency of these “freckles” in melanoma patients and controls have clearly demonstrated that freckles are an independent risk factor for melanoma (7). The density of freckling has been related to the underlying genotype of the patient for the so-called “freckle gene,” the melanocortin receptor MC1R (8) (which also controls skin, hair, and eye color) (9). Patients with certain haplotypes of MC1R have increased freckles and increased risk for melanoma. Other haplotypes may be associated with increased melanoma risk but not with freckling.

Histologically, in biopsy specimens and also in reexcision specimens for melanoma, it is important not to overinterpret an actinic lentigo as a melanoma because of the presence of an increased number of melanocytes. Differences between lentigines and melanomas include the following: (1) In general, actinic lentigines are smaller than melanomas, although there are occasional examples of very large actinic lentigines that tend to attract clinical scrutiny and be submitted for biopsy. (2) Although melanocytes are increased they are not in contiguity with one another. (3) Pagetoid scatter of atypical melanocytes into the epidermis is minimal or absent. (4) Melanocytic atypia is mild to moderate and “random” and is present in a minority of the lesional cells rather than in the majority of them. (5) There may be a host response to melanoma in the form of a lymphocytic infiltrate or diffuse fibroplasia. These changes are absent in actinic lentigines. In each case, there is
usually at least moderate or severe actinic elastosis in the dermis.

In cases of very large actinic lentigines, sometimes present in cosmetically significant locations on the face such as the eyebrows or eyelids or near the lips, establishing a definitive diagnosis can be difficult. Often punch biopsies are taken as a sampling of the lesion; however, it cannot necessarily be assumed that a punch biopsy is representative of the entire lesion. There are examples of unquestioned lentigo maligna melanomas that have regions within them that are indistinguishable from actinic lentigines, which may represent a precursor lesion.

It is generally agreed that actinic lentigines may evolve into benign lichenoid keratoses, lesions that are characterized by lichenoid inflammation at the dermal–epidermal junction, and perhaps by regression of the preexisting lesion (10). There has been debate over many years whether actinic lentigines are precursor lesions of lentigo maligna melanoma (10,11). This is complicated by the fact that actinic lentigines are so numerous in chronically sun-damaged skin that any melanoma is likely to “overrun” a preexisting actinic lentigo, or more than one of these ubiquitous lesions. In one study, a solar lentigo was seen in contiguity with a lentigo maligna melanoma in 30% of cases, suggesting a precursor lesion and also raising the issue of sampling error in biopsies. In addition, there seem to be examples of lesions that are intermediate or borderline between actinic lentigo and lentigo maligna melanoma, suggesting that the progression paradigm is real. This, of course, does not mean that actinic lentigines should be excised in an effort to prevent melanoma; rather these observations support the epidemiologic evidence that they should be regarded as markers of increased risk for melanoma, especially of the lentigo maligna subtype (12). When there is also nuclear atypia of scattered lesional cells within lentigines or within skin showing severe chronic solar damage, we regard this as a “field effect,” and as an indicator of skin that is likely to be at increased risk for development of atypical melanocytic proliferations including possibly melanomas in the future. Patients with these findings should likely be offered skin surveillance in an effort to diagnose any melanomas at an early, curable stage. At the same time, histologic interpretation of lesions excised should be parsimonious in an effort not to increase the already prevalent problem of “overdiagnosis” of melanoma, which can lead to overtreatment and to distortion of public health statistics.

Atypical lentigines also overlap with lentiginous junctional and compound nevi that may occur in skin with chronic solar damage, usually in elderly patients. The “atypical lentiginous nevus in the elderly” may be regarded as a form of dysplastic nevus, or as a lesion occupying a parallel position to the dysplastic nevus (a low-intermediate CSD lesion) in a high CSD environment. In a study of 14 cases, most of the patients were over 50 years of age. Clinically the lesions resembled atypical nevi and they were all located on the back. Histologically they had irregular lentiginous epidermal hyperplasia with proliferation of individual melanocytes in the basal layer of the epidermis. Dermal nests were absent. Upward migration of melanocytes into the epidermis was focal, or absent in most cases. There was cytologic atypia, which was moderate in most of the cases. The Ki-67 proliferation index was low. There were no instances of recurrence in a relatively short follow-up interval (13). In another study of nevi from elderly patients, 215 nevi from 172 patients 60 years of age or older were reviewed histologically. The lesions were frequently junctional and a lentiginous often heavily pigmented growth pattern was commonly seen. Severely atypical (dysplastic) changes were found in 6% of the lesions. It was concluded that benign junctional nevi were relatively common in older patients, and that
these lesions must be differentiated from dysplastic nevus and melanoma in situ, with which they overlap morphologically (14). These lesions overlap in particular with CSD melanomas that have features overlapping with dysplastic nevi, known as “nevusoid lentigo maligna” (15), “dysplastic nevus-like melanoma” (16), and/or “lentiginous melanoma” (17), as discussed in the previous section.

References
2.2.1

Actinic Lentigo Versus Lentigo Maligna

**Clinical Information**
F64 back. Favor solar keratosis over lentigo maligna.

**Reason for Consultation**
I favor a solar lentigo, although there are occasional atypical melanocytes—what do you think?

**Description**
These sections show a superficial shave biopsy in sun-damaged skin, containing an ill-defined, poorly circumscribed quite broad lesion characterized by hyperpigmentation of basal keratinocytes, elongation of rete ridges, and an increased number of basal melanocytes, which are present as single cells near the dermal-epidermal junction.

**Figure 2.2.1.1** A broad, superficial shave biopsy in skin with severe chronic solar damage.

**Figure 2.2.1.2** There is slight elongation of rete ridges and there is hyperpigmentation of basal keratinocytes.

**Figure 2.2.1.3** In this field there is slight prominence of basal melanocytes, which are present as single cells near the dermal-epidermal junction.
slightly to moderately enlarged nevoid to epithelioid melanocytes, mostly near the dermal–epidermal junction as single cells. A few of them have somewhat enlarged and slightly hyperchromatic nuclei consistent with mild random cytologic atypia. There is no clear evidence of continuous basal proliferation of uniformly atypical cells and there is no extensive high-level pagetoid proliferation. I will order Melan-A and MITF stains to assess for confluence, and report the results later. For the present, I will interpret this lesion descriptively as follows:

**PROVISIONAL DIAGNOSIS**

Skin, site not stated: Intraepidermal atypical melanocytic proliferation of uncertain significance, see Description and Comment.

**COMMENT 1**

Like you, I would favor an actinic lentigo with atypia of the type that may be seen in chronically sun-damaged skin and likely represents a field effect indicative of skin at risk for melanocytic and other neoplasia. We will review Melan-A and MITF stains and report the findings as an addendum.

**COMMENT 2 (A FEW DAYS LATER)**

Immunostains have been reviewed. Although the Melan-A shows quite strong staining along the junction, much of this reactivity represents staining of dendrites rather than contiguous cell bodies. MITF demonstrates only a subtly increased number of melanocytes at the interface, if at all. These changes are therefore consistent with an actinic lentigo. I would therefore amend the diagnosis as follows:

**FIGURE 2.2.1.4** A Melan-A stain demonstrates strong seemingly continuous staining in the basal layer of the epidermis.

**FIGURE 2.2.1.5** In an MITF stain, although there is some background staining of keratinocytes, the specific stain demonstrates that the melanocytes, while increased in number, are separated by basal keratinocytes and therefore there is no evidence of continuous basal proliferation.
2.2.1

**FINAL DIAGNOSIS**

Skin, site not stated: Actinic lentigo with mild to moderate atypia, see Description and Comment.

**COMMENT**

The atypia is of the degree that can be seen in chronically sun-damaged skin, and likely represents a risk factor for melanocytic neoplasia. Continuing follow-up may therefore be appropriate (MPATH DX Category 1).

**OVERALL COMMENT**

Changes of actinic lentigo are commonly seen in melanoma reexcision specimens and should not be overinterpreted as melanoma in situ. These changes may be regarded as a “field effect,” and a risk factor for future development of atypical melanocytic lesions. Occasionally, a large actinic lentigo, as in this case, represents the clinical indication for a biopsy procedure, usually to rule out melanoma.
2.2.2

Actinic Lentigo Versus Lentigo Maligna

CLINICAL INFORMATION
Right cheek lesion in a 55-year-old woman

REASON FOR CONSULTATION
I have enclosed a representative slide for your review and opinion.

DESCRIPTION
These sections show a biopsy of skin with severe actinic elastosis, within which there is a quite broad lesion characterized by hyperpigmentation of basal keratinocytes with an increased number of melanocytes. Although increased in number, the cells are not arranged in nests or in continuous basal patterns, and cytologic atypia is minimal and random. In summary, I would interpret this material as follows:

FIGURE 2.2.1 A broad biopsy of chronically sun-damaged skin within which there is a region of thickening of the epidermis with elongated rete ridges.
FIGURE 2.2.2.2 and FIGURE 2.2.2.3 There is also hyperpigmentation of basal keratinocytes.

FIGURE 2.2.2.4 Focally there is an increased number of melanocytes in the basal epidermis, but there is no evidence of continuous basal proliferation or of severe uniform atypia.
**DIAGNOSIS**

Skin, right cheek: Actinic lentigo, see Description and Comment.

**COMMENT**

I see no evidence of malignancy in this lesion. Changes extend close to one specimen margin; however, the lesion appears to be essentially excised. There is residual clinically atypical lesion and especially if there had been dynamic changes in it, complete excision to rule out additional significant pathology may be appropriate.

**OVERALL COMMENT**

There is no severe atypia in this lesion, although there is severe actinic elastosis and if only for this reason, surveillance might be considered, with no additional therapy for this lesion (MPATH DX Category 1).
2.2.3

Actinic Lentigo With Spindle Cells

**Clinical Information**
Multiple slides from several procedures done over 6 years on lesions of the right upper arm in a 56-year-old woman.

**Reason for Consultation**
Please review outside slides and reports.

**Description**
In the first biopsy, there is hyperpigmentation of basal keratinocytes without melanocytic proliferation or atypia. There is moderate actinic elastosis in the dermis and these changes are consistent with an actinic lentigo. Focally, there is an increased number of delicate spindle cells with a few scattered lymphocytes.

**Figure 2.2.3.1** A broad and deep shave biopsy of skin.

**Figure 2.2.3.2** Toward one periphery, the epidermis appears unremarkable.

**Figure 2.2.3.3** Throughout much of the lesion, there is hyperpigmentation of basal keratinocytes without prominent melanocytic proliferation.
CASE 3: ACTINIC LENTIGO WITH SPINDLE CELLS

2.2.3

**FIGURE 2.2.3.4** In the dermis there are a few inconspicuous histologically bland spindle cells. There is no histologic evidence of malignancy.

**FIGURE 2.2.3.5** Six years later, a tumor had developed at or near the site of the prior biopsies. The tumor appears to arise in the mid-dermis and to extend into the subcutis.

**FIGURE 2.2.3.6** The tumor is comprised of spindle cells and there are nodular clusters of lymphocytes.

**FIGURE 2.2.3.7** The spindle cells are atypical and infiltrate septa of the panniculus as well as fat lobules.

in the papillary dermis. Given the history that this is a recurrent lesion, these could reasonably be interpreted as a reaction to the prior biopsy at this site. There is no other evidence of a biopsy site reaction in this material.
Seven years after this first biopsy was reviewed and reported as an actinic lentigo at an outside institution, a large tumor developed at or near the same site and on review was interpreted as follows:

**FINAL DIAGNOSIS**

Mass, left shoulder, excision. Malignant spindle cell tumor, consistent with desmoplastic melanoma, nonulcerated, tumorigenic, Clark level V, Breslow thickness at least 7 mm, present at specimen base, see Description and Comment.

**COMMENT**

It is not possible to make a diagnosis of malignant melanoma in the first specimen received for review, which histologically has the appearance of an actinic lentigo. There were a few spindle cells in the dermis (recognized with hindsight), but these could be explained by the information that this lesion was recurrent at that time.

**OVERALL COMMENT**

As reviewed above, actinic lentigines can be both precursors and risk markers for melanoma, usually of the lentigo maligna type. In this particular case, a desmoplastic melanoma developed near the same site 6 years later. There is no connection to the overlying epidermis so it is not possible with this material to draw a continuous link between the two conditions and it therefore could be possible and perhaps more likely that the desmoplastic melanoma was coincidental or represented an example of a field effect creating increased risk for an independent primary lesion, and not a direct recurrence of the preexisting lentigo. The initial lesion could be treated by observation or by narrow local excision (MPATH DX Category 1 or 2). The recurrent (or coincidentally newly evolved) melanoma, of course, would be Category 5.
2.2.4

Atypical Lentigo Versus Regressing Melanoma

**Clinical Information**
Atypical nevus of the upper arm in a 45-year-old man.

**Reason for Consultation**
This was sent in as an atypical nevus—I am seeing a moderately atypical junctional nevus with a dense perivascular infiltrate consistent with a halo phenomenon. What do you think?

**Description**
These sections show a junctional pigmented lesion, which is quite small (less than 3 mm), and generally moderately cellular. There are two major components. One of these is a region of elongated rete ridges with an increased number of small nevoid melanocytes arranged mainly near the sides and tips of the rete, with only minimal nest formation, consistent

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**Figure 2.2.4.1** A broad lesion with two separate components, one with effaced rete ridges and a bandlike lymphocytic infiltrate and the other with elongated rete ridges.
Figures 2.2.4.2–2.2.4.4 In the region of the bandlike lymphocytic infiltrate, there is atypia of keratinocytes in the overlying epidermis and there is parakeratosis. There is also hyperpigmentation and there are some dendritic melanocytes within the atypical proliferation.

Figures 2.2.4.5 and 2.2.4.6 In this region of the lesion there are elongated rete ridges, hyperpigmentation of basal keratinocytes, and an increased number of melanocytes, with actinic elastosis in the underlying dermis, consistent with an actinic lentigo.
with a lentiginous junctional nevus or simple lentigo. Contiguous with this, there is a region where there is a brisk bandlike lymphocytic infiltrate and diffuse fibroplasia in the papillary dermis, and in this region there is cytologic atypia of cells in the basal layer of the epidermis, which is markedly attenuated, with overlying parakeratosis. In this region there is evidence of melanocytic proliferation in the form of pigmented dendrites. However, I believe that the atypical cells in the keratinocytes and the dendritic melanocytes are likely to be reactive. There is mild to moderate actinic elastosis in the dermis, and I believe the changes are those of a pigmented actinic keratosis in collision with an actinic lentigo.

**DIAGNOSIS**

Skin, site not stated: Actinic keratosis, pigmented, in contiguity with an actinic lentigo.

**COMMENT**

As discussed above, I would consider this to be a combination of an actinic lentigo and an actinic keratosis, two lesions that are common, of course, in chronically sun-damaged skin. One might also consider a benign lichenoid keratosis. I do not believe there is significant melanocytic atypia in this lesion. Reexcision is not necessary if the biopsy is representative (MPATH DX Category 1).
2.2.5

Lentiginous Nevus Versus Lentiginous Melanoma

CLINICAL INFORMATION

A large pigmented lesion of the back in a 74-year-old man.

REASON FOR CONSULTATION

I called this lesion a dysplastic nevus. The clinician then calls back to inform us that this is a 2.2 cm irregular pigmented lesion. Now looking at the deepers we think this might be a “lentiginous melanoma.”

DESCRIPTION

These sections show a shave biopsy of skin containing a relatively sparsely cellular, fairly broad, rather poorly circumscribed lesion in the skin with moderate actinic elastosis. The lesion is comprised of single and a few nests of melanocytes arranged mainly near the tips and sides of elongated rete ridges, with a few nests bridging between adjacent rete. Cytologically, there is moderate nuclear enlargement and irregularity of...
a few randomly scattered lesional cells. In another area, there is effacement of the rete ridge pattern, with continuous proliferation of single cells along the junction. There is a suggestion of fibrosis in the dermis centrally, and I wonder if this lesion has been previously biopsied or treated perhaps with cryotherapy. In any event, I would agree that the differential diagnosis lies between a moderately to severely
dysplastic nevus, a “lentiginous nevus of the elderly” with atypia, and a nevoid lentigo maligna or lentiginous melanoma. The most atypical area seems to be related to the fibrosis in the dermis, raising the question of a component of “recurrent nevus,” with an adjacent “persistent nevus.” Because of all these difficulties of interpretation, I would interpret this lesion descriptively as follows:

### DIAGNOSIS

Skin, midback: Superficial atypical melanocytic proliferation of uncertain significance, most consistent with melanoma in situ, lentiginous type (nevoid lentigo maligna), see Description and Comment.

### COMMENT

In the absence of clear evidence of invasion of the dermis and certainly in the absence of tumorigenic or mitogenic activity in the dermis, this is a lesion that I would not expect to have any competence whatsoever for metastasis. Because of the differential diagnosis of a lentiginous melanoma, the possibility of a lesion with potential for persistence, recurrence and future progression cannot be ruled out. I would therefore recommend managing this lesion according to protocols for melanoma in situ, or at least by complete local excision (MPATH DX category 2 or 3). I would be interested to hear if there is any history of prior destructive/ablative therapy or biopsy at this site.

### OVERALL COMMENT

As discussed in the introduction, there are overlapping features among atypical actinic lentigines, lentiginous junctional nevi with and without atypia, and lentiginous or “nevoid” lentigo maligna. Lesions in a high CSD environment must be interpreted with circumspection. However, overdiagnosis should also be avoided as lentiginous junctional nevi of the elderly seem to be biologically benign. Nevertheless, it would seem to be judicious to completely excise these lesions in order to be sure that they have been completely examined histologically and also to preclude any possibility of local persistence, recurrence, or future progression.
3.0 Superficial Atypical Melanocytic Proliferations in Acral Skin

3.1 Acral Melanoma
   3.1.1 Acral Melanoma Versus Acral Nevus
   3.1.2 Acral Melanoma In Situ Versus Atypical Melanocytic Hyperplasia
   3.1.3 Acral-Lentiginous Melanoma
   3.1.4 Acral Melanoma Present at Specimen Margin
   3.1.5 Acral Melanoma With Multiple Recurrences
   3.1.6 Acral Junctional Nevus Versus Acral Melanoma

3.2 Special Site Nevi and Other Atypical Proliferations of Acral Skin
   3.2.1 Acral-Lentiginous Nevus Versus Acral-Lentiginous Melanoma In Situ
   3.2.2 Acral-Lentiginous Nevus Versus Acral-Lentiginous Melanoma
   3.2.3 Acral Nevus Versus Dysplastic Nevus Versus Melanoma
   3.2.4 Acral Versus Spitz Versus Dysplastic Nevus
   3.2.5 Acral Nevus Versus Lentigo, Atypical
   3.2.6 Acral Nevus Versus Lentigo
   3.2.7 Atypical Nevus Versus Melanoma
Acral skin is highly specialized and is protected from sun exposure because UV light is diffused by the thick stratum corneum. Acral melanomas and nevi therefore represent “no chronic solar damage (no CSD)” melanocytic proliferations.

This important difference is also accompanied by differences in morphology and in the genetic underpinnings of the tumors. Acral nevi have been included in the general category of “special site nevi,” because they characteristically express morphologic features (such as pagetoid scatter of lesional cells into the epidermis) that may be seen in melanomas, leading to difficulty in the differential diagnosis.

Acral melanomas have been found to contain mutations of oncogenes that differ from those of the common superficial spreading “low CSD” melanomas and also, to some extent, from the “high CSD” lentigo maligna melanomas. Interestingly, the oncogene KIT tends to be mutated both in the acral lesions and in mucosal melanomas, which may also have a lentiginous in situ component (1,2). Only the acral lesions, however, show common abnormalities of cyclin D, including amplifications and mutations of this important cell cycle gene (3).
Melanoma occurring in acral skin has special features and these lesions were originally described as “plantar lentiginous melanoma” in 1977 (4), and then as “acral-lentiginous melanoma” (5). It was recognized that these lesions were the most frequent subtype of melanoma in people of African ancestry and then later in Asian and other populations (6–8). The reason for this increased relative frequency is the fact that other forms of melanoma, namely for the most part those related to sun exposure, are rare in these populations. In fact, the absolute incidence of acral melanoma is about the same in all populations (7).

The etiology is unknown, with trauma, chronic irritation, or physical stress having been considered as a leading possibility in a recent study of 177 acral melanomas from South Korea (9).

Many of these acral melanomas exhibit a lentiginous pattern characterized by a continuous proliferation of single cells along the dermal–epidermal junction, hence the name “acral-lentiginous melanoma.” Although sharing the property of lentiginous proliferation, these lesions are very different from lentigo maligna melanoma, which occurs in skin with severe chronic solar damage. In contrast, acral skin does not suffer from solar damage as discussed above. This lentiginous proliferation is a feature of the radial growth phase. The vertical growth phase of these melanomas is similar in general to those of other sites although more likely to be comprised of spindle cells and to be associated with a desmoplastic and neurotropic vertical growth phase. Although acral-lentiginous melanomas were often diagnosed at an advanced stage, the prognosis is not worse than that of other melanomas when thickness and other risk factors are controlled (10). These lesions occurred in plantar skin more frequently than in skin of the palms, and most frequently on the great toe (9). They could also occur in a subungual location, again most commonly on the great toe (11).

Even though the pathogenesis of acral melanomas remains unclear, long-term physical stress or pressure strength can influence the incidence and spreading pattern (9,11).

Bastian and others have demonstrated that melanomas in acral skin share common genetic abnormalities, often involving amplification and sometimes mutation of cyclin D, or amplification and mutation of the oncogene KIT (12–15). According to Bastian’s observations, these genomic changes are not necessarily associated with lentiginous proliferation and are shared by some pagetoid melanomas that also occasionally occur in acral skin. For this reason, the recent WHO classification used the term “acral melanoma” rather than “acral-lentiginous melanoma” (16). In my opinion, it is still reasonable to use this terminology when a lentiginous pattern is seen. This lentiginous pattern can be subtle with poor circumscription at the periphery and is often amelanotic, factors that can lead to problems with evaluation of specimen margins both clinically and histologically. Amelanotic acral melanomas, which show rare or absent brown to black pigmentation

### 3.1 Acral Melanoma
in the lesion, are rare and difficult to diagnose both clinically and pathologically. In a study of 35 cases of amelanotic acral melanomas, 26 cases were located on the feet, and 16 cases were developed in subungal areas. Nodular melanoma was the most common histopathologic subtype. HMB 45 staining was sometimes negative. KIT mutation was detected in four cases (12.1%), and all of them showed no pigment at all (17). The lentiginous morphology is highly characteristic of acral melanomas and is also seen in so-called “special site nevi” of acral skin, which will be more fully discussed in the next section. In my experience, pagetoid melanomas tend to be more heavily pigmented, even when they occur on ankle skin.

The general principles of management of acral melanoma are similar to those for other melanomas. Most lesions when in situ can be managed as MPATH DX Category 3 and when invasive as Categories 4 or 5 (see Introduction). Wide excision with standard margins may result in serious functional defects and/or delayed wound healing problems because the foot is a weight-bearing area and there is no elastic normal skin around the melanoma. Various surgical methods, such as free flap, skin graft, and secondary healing are used.

References
3.1.1

Acral Melanoma Versus Acral Nevus

**CLINICAL INFORMATION**
Seventy-four-year-old woman with an atypical pigmented lesion of heel, t/o melanoma.

**REASON FOR CONSULTATION**
There is a subtle lentiginous proliferation with atypia; clinical photo suggests melanoma.

**FIGURE 3.1.1.1** A punch biopsy of skin from a clinically atypical lesion of the heel of a 74-year-old woman. There is hyperpigmentation mainly of basal keratinocytes and there is increased cellularity along the junction.

**FIGURE 3.1.1.2** There is a subtle increase of melanocytes along the dermal–epidermal junction without extensive continuous basal proliferation.

**FIGURE 3.1.1.3** There is a subtle increase of melanocytes along the dermal–epidermal junction without extensive continuous basal proliferation.

**FIGURE 3.1.1.4** The subtle changes extend to the inked specimen margin.
3.1.1

**FIGURE 3.1.1.5** Melan-A staining demonstrates somewhat more numerous melanocytes than could be appreciated in the H & E stain.

**DESCRIPTION**
Sections of the punch biopsy show, as you have described, a relatively subtle proliferation of dendritic melanocytes along the dermal–epidermal junction. There is slight to moderate atypia in the form of enlargement and slight hyperchromatism of some of the lesional cells. There are no well-developed nests. There is no substantial pagetoid proliferation into the epidermis and no evidence of invasion of the dermis. Taken in isolation, I would agree with your interpretation of this biopsy as follows:

**DIAGNOSIS**
Skin, right heel: Atypical intraepidermal lentiginous melanocytic proliferation, extending to specimen margins.

**COMMENT**
A clinical photograph was also made available for review. In my opinion, this image shows changes consistent with melanoma in situ of the acral-lentiginous type. Taken in conjunction with the findings in this biopsy, I believe that the clinical findings and the histologic findings reviewed together are diagnostic of melanoma, at least in situ. Of course, the possibility of invasion elsewhere in the lesion cannot be ruled out. One would ordinarily recommend complete excision of a lesion of this type; however, this could possibly be modified by major health considerations of the type mentioned in one of your reports (MPATH DX Category 2 or 3).

**OVERALL COMMENT**
Clinicopathologic correlation can be of great assistance in supporting a histologic diagnosis of melanoma; however, one must be certain that the histopathologic findings are at a minimum consistent with the diagnosis that is being made. If not, additional biopsies should be obtained.
3.1.2

Acral Melanoma In Situ Versus Atypical Melanocytic Hyperplasia

**Clinical Information**
A 61-year-old man with melanoma of left heel.

**Reason for Consultation**
Wide excision of left heel melanoma and sentinel lymph node biopsy. Prior biopsy showed malignant melanoma, nonulcerated, Clark’s level IV, Breslow thickness 3.2 mm, with a mitotic rate of 8/mm². Please evaluate specimen margins.

**Figure 3.1.2.1** An excision specimen containing a broad lesion in acral skin characterized at scanning magnification by patchy focally dense aggregates of lymphocytes and the increased cellularity along the junction.

**Figure 3.1.2.2**

**Figure 3.1.2.3**

**Figures 3.1.2.2 and 3.1.2.3** There is a marked increase of cells along the junction with extensive areas of continuous basal proliferation.
3.1.2

**DESCRIPTION**

These sections show a broad, quite highly cellular lesion characterized in this material by proliferation of nevoid to epithelioid melanocytes, arranged predominantly near the dermal–epidermal junction, with areas of continuous basal proliferation. There is also pagetoid scatter of some lesional cells in focal areas. Cytologically, there is moderate to severe atypia, which is relatively uniform in some areas, meaning that greater than 50% of the cells showed atypia in the form of nuclear enlargement, irregularity, and hyperchromatism. There is also a focally lichenoid and also perivascular to diffuse focally quite dense lymphocytic infiltrate in the dermis. As is usual in an acral site, solar elastosis is not observed.

**FIGURE 3.1.2.4** There is also pagetoid scatter of cells into the epidermis, which, although not a prominent feature across the lesion, is diagnostically helpful. There is also moderate to severe atypia of lesional cells, which is relatively uniform in some areas although in other areas there are lesional cells with small relatively inconspicuous nuclei.

**FIGURE 3.1.2.5** The atypical changes extend to an inked specimen margin. This lesion was amelanotic, at least in these peripheral sections, and the borders were not readily visualized clinically.

**DIAGNOSIS**

Skin, left heel, wide excision: Residual melanoma in situ present at inked anterior resection margin, no residual invasive malignant melanoma seen; other margins of resection free of involvement (less than 1 mm from inferior margin).

**COMMENT**

As noted above, there is a positive specimen margin involved by acral-lentiginous melanoma in situ.

**OVERALL COMMENT**

Obtaining clear margins in acral melanomas can be difficult for several reasons including perhaps reluctance to accept an extremely wide excision on weight-bearing skin, and also because often the in situ melanoma at the periphery of the lesion is amelanotic and its borders are difficult to discern clinically. This lesion was invasive elsewhere (MPATH DX Category 5).
3.1.3

**Acral-Lentiginous Melanoma**

**CLINICAL INFORMATION**
Prior punch biopsy showed malignant melanoma, ulcerated, Breslow thickness not less than 2.1 mm, extending to the specimen base. Amputation specimen of right third, fourth, and fifth toes and forefoot, containing a variegated pigmented lesion 3.2 cm in diameter, with an ulcerated nodule 1.8 cm in diameter in the center of the specimen.

**REASON FOR CONSULTATION**
Please review and confirm diagnosis.

*FIGURE 3.1.3.1* There is a bulky tumor extending into the subcutis. Adjacent to it there is an atypical intraepidermal melanocytic proliferation.

*FIGURE 3.1.3.2* This proliferation extends far into the adjacent skin.
section 3.1: acral melanoma

3.1.3

FIGURE 3.1.3.3 and 3.1.3.4 There is a moderately dense lymphocytic infiltrate with fibroplasia in the dermis and with pigmented melanophages. In the epidermis there is a markedly increased number of melanocytes, present as single cells with a few nests, predominantly near the dermal–epidermal junction but with suprabasal scatter generally to the lower third. Cytologic atypia in these images is generally moderate.

FIGURE 3.1.3.5 In other areas the cellularity is greater, with more severely and uniformly atypical nevoid to epithelioid melanocytes exhibiting continuous basal proliferation, irregular nest formation, and pagetoid scatter into the epidermis.
DESCRIPTION
Sections of the ulcerated nodule show a bulky tumor comprised of uniformly atypical epithelioid to spindled melanocytes extending from an ulcerated surface into the subcutis. There are frequent mitoses. Sections of the adjacent skin demonstrate extensive changes including fibrosis and inflammation in the dermis, with pigmented melanophages. In the epidermis in these regions, there is hyperpigmentation and increased numbers of nevoid to epithelioid melanocytes present in a continuous pattern along the junction and extending into the epidermis in a pagetoid scatter pattern generally not beyond the lower third. These changes are diagnostic of acral-lentiginous melanoma in situ. Sections of the specimen margins are free of involvement by in situ or invasive melanoma.

COMMENT
The dermal mitotic rate in the vertical growth phase is 10/mm². There is an ulcer that measures greater than 1 cm in diameter. Tumor-infiltrating lymphocytes are sparse in relation to the vertical growth phase. There is no radial growth phase regression, and no associated nevus. There is evidence of lymphovascular and perineural invasion. Excision is complete with clear margins in this amputation specimen.

OVERALL COMMENT
This lesion presents little diagnostic difficulty and is presented as a bona fide example of acral melanoma in situ with a predominantly lentiginous pattern, adjacent to an ulcerated tumorigenic and mitogenic vertical growth phase (MPATH DX Category 5).

DIAGNOSIS
Foot, right third, fourth, and fifth toes, amputation: Malignant melanoma, acral type, Clark level V, Breslow thickness 4.7 mm, tumorigenic and mitogenic, ulcerated, adjacent in situ melanoma, see Description and Comment.
3.1.4

Acral Melanoma Present at Specimen Margin

**Clinical Information**

Outside slides for review from melanoma reexcision specimen, left heel wide excision of a 78-year-old man.

**Reason for Consultation**

Confirm diagnosis, please evaluate margins.

**Figure 3.1.4.1** A broad region of involvement of acral skin by a markedly cellular proliferation of nevoid to epithelioid melanocytes

**Figure 3.1.4.2** The lesional cells are arranged as irregularly oriented nests and also as single cells, mainly near the dermal–epidermal junction. There is moderate uniform atypia.

**Figure 3.1.4.3** In another region of the specimen closer to its periphery there is a more subtle proliferation of smaller nevoid to epithelioid melanocytes.
3.1.4

CASE 4: ACRAL MELANOMA PRESENT AT SPECimen MArgin

DESCRIPTION

Sections show a very broad region of involvement by a markedly cellular proliferation of nevoid to epithelioid melanocytes. These are arranged as nests that are irregularly distributed along the dermal–epidermal junction in acral skin, and also as single cells with pagetoid scatter generally in the lower to middle thirds of the epidermis. There is no evidence of invasion of the dermis in this material. Margin specimens from medial and superior margins of resection contain moderately to highly cellular proliferation of uniformly atypical cells consistent with melanoma in situ. The central portion of the specimen is extensively involved by melanoma in situ, which is essentially amelanotic.

FIGURES 3.1.4.4 and 3.1.4.5 These small lesional melanocytes exhibit mild atypia in the form of nuclear irregularity and slight enlargement. They are present in a patchy arrangement along the dermal–epidermal junction, and there is pagetoid scatter into the epidermis. Lesional cells are present at the inked specimen margin.

DIAGNOSIS

Skin, left heel, wide excision: Skin with residual melanoma in situ, acral-lentiginous type, involving medial and superior margins of resection.

COMMENT

The changes at the specimen margin could overlap with findings in some acral “special site” nevi; however, their presentation as a component of a much larger lesion with findings diagnostic of melanoma in situ indicates that they must be regarded as representing melanoma in situ, present at the specimen margin.

■ OVERALL COMMENT ■

Evaluation of margin specimens from amelanotic melanomas in general can be difficult. This problem is more often seen in acral and other lentiginous melanomas than in pagetoid superficial spreading melanomas, which are more often pigmented, and also comprised of larger cells with a greater tendency to nesting. This lesion is invasive elsewhere (MPATH DX Category 5).
3.1.5

Acral Melanoma With Multiple Recurrences

CLINICAL INFORMATION
Please review the slides from this 78-year-old patient referred to our clinic. She has had multiple recurrences of acral melanoma over 14 years. The original melanoma was invasive to Clark’s level III, Breslow thickness 1.8 mm. These slides are not available for review.

REASON FOR CONSULTATION
Do you agree with the diagnosis?

FIGURE 3.1.5.1

FIGURES 3.1.5.1 and 3.1.5.2 Sections of the initial reexcision specimen show acral skin involved by a moderately cellular proliferation of nevoid melanocytes characterized by cytologic atypia albeit mild to moderate and present in a more or less continuous pattern along the dermal–epidermal junction. There was a biopsy site reaction consistent with a prior biopsy, which was not available for review.
FIGURES 3.1.5.3 and 3.1.5.4  Sections of the first recurrence from 10 years later show similar changes with somewhat greater atypia and with pagetoid scatter of lesional cells into the lower levels of the squamous epithelium.

FIGURES 3.1.5.5 and 3.1.5.6  In these sections from the second recurrence 2 years later there is a subtle increase of melanocytes along the dermal–epidermal junction, present at a blue inked margin.
3.1.5

**Figure 3.1.5.7**

**Figure 3.1.5.8**

**Figures 3.1.5.7 and 3.1.5.8** Melan-A staining of the lesion seen in Figure 3.1.5.5 highlights the increased number of melanocytes; however, these have retained dendrites and lack nesting as well as continuous basal proliferation. Cytologic atypia is minimal.

**Figure 3.1.5.9**

**Figure 3.1.5.10**

**Figures 3.1.5.9 and 3.1.5.10** This latest biopsy from 2 years later was from a region of hyperpigmentation; however, there is no definitive increase of melanocytes except for a few cells clustered around the third rete ridge from the left in image number 10.
DESCRIPTION
Sections of the initial reexcision specimen show an extensive region of involvement of the epidermis by an increased number of nevoid to epithelioid melanocytes arranged singly, predominantly near the dermal–epidermal junction, with extensive continuous basal proliferation and with uniform albeit moderate cytologic atypia, diagnostic of acral-lentiginous melanoma in situ. These findings are adjacent to a biopsy site reaction from the lesion that had been diagnosed as invasive melanoma, not available for review.

Sections of the second specimen from 10 years later show somewhat more subtle but definitely increased number of single melanocytes along the dermal–epidermal junction, with mild to moderate cytologic atypia and with pagetoid scatter into the lower third of the epidermis. These changes are diagnostic of acral-lentiginous melanoma in situ, recurrent by history.

Sections from the specimen of 2 years later show a punch biopsy of skin containing a subtle increase of lesional melanocytes adjacent to an inked specimen margin. A Mart stain is available and demonstrates an increased number of melanocytes at the inked margin. These appearances are not diagnostic of melanoma in situ and are interpreted as intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPS).

Sections of the latest specimen show a punch biopsy of skin, containing a few small melanocytes focally increased in number. These changes are not diagnostic of melanoma in situ.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>First specimen: Melanoma in situ, acral-lentiginous type, residual adjacent to a prior biopsy site reaction.</td>
</tr>
<tr>
<td>Second specimen: Melanoma in situ, acral-lentiginous type, recurrent by history.</td>
</tr>
<tr>
<td>Third specimen: IAMPS, clinically recurrence at the site of prior acral-lentiginous melanoma.</td>
</tr>
<tr>
<td>Latest specimen: Subtle intraepidermal proliferation of cytologically mature melanocytes, of uncertain significance, see Description and Comment.</td>
</tr>
</tbody>
</table>

COMMENT
The appearances suggest that these findings may represent a “field effect” of melanocytic atypia in the region of prior occurrence of a melanoma. The clinical recurrences have shown decreasing degrees of atypia and it has been decided to follow this patient closely, rather than to radically excise this important region of weight-bearing skin.

OVERALL COMMENT
Bastian has presented a concept of “field cells” that have cytogenetic abnormalities demonstrable by fluorescence in situ hybridization, while lacking morphological evidence of melanoma (13). It is possible that these recurrences over a period of more than 14 years might be related to this phenomenon. It is difficult to recommend management for a case like this, although typically the in situ lesions would be excised with at least 5 mm margins (MPATH DX Category 3).
CLINICAL INFORMATION
F 61. Lesion of the right sole. Irregular dark macule, rule out atypia.

REASON FOR CONSULTATION
I would appreciate your opinion and thoughts on further management of this lesion. My opinion is as follows:

Severely atypical junctional acral melanocytic proliferation, extending to the lateral and focally to the deep margin. This is a borderline lesion for which in my opinion the differential includes a junctional lentiginous acral nevus with severe atypia and an early malignant melanoma in situ. Concerning features include the presence of fairly broad, disorganized junctional growth, single cell predominance with focal near confluent growth, and fairly prominent pagetoid extension. However, in view of the borderline nature of this lesion and the challenges associated with the interpretation of atypical lentiginous acral melanocytic proliferations, a consultative opinion will be requested.

FIGURE 3.1.6.1 A superficial biopsy showing a broad lesion with an asymmetrical architecture at scanning magnification.
CASE 6: ACRAL JUNCTIONAL NEVUS VERSUS ACRAL MELANOMA

3.1.6

FIGURES 3.1.6.2 and 3.1.6.3 There is a moderately cellular proliferation of single cells and a few nests near the dermal–epidermal junction and above it.

FIGURES 3.1.6.4 and 3.1.6.5 Lesional cells exhibit generally moderate but quite uniform cytologic atypia.

DESCRIPTION

These sections show a moderately to highly cellular proliferation of nevoid to epithelioid and dendritic cells, arranged singly and in a few ill-defined nests along the dermal–epidermal junction. There is also pagetoid scatter into the epidermis. Cytologically, there is what I would characterize as moderate to focally severe and relatively uniform atypia in the form of nuclear enlargement, irregularity, and nucleoli. Given the considerable breadth of this lesion, variable cellularity across it, the cytologic atypia, and the pagetoid scatter, even though the latter may be seen in acral nevi, and also taking into consideration the clinical description and the age of the patient, I believe this lesion must be regarded as a melanoma, which I would characterize as follows:
3.1.6

**COMMENT**

I would, of course, recommend definitive excision of this lesion, and follow-up for the patient (MPATH DX Category 3).

**OVERALL COMMENT**

This lesion is more sparsely cellular than most acral melanomas in situ; however, in my opinion there is no other possible diagnosis. Definitive therapy is indicated to prevent possible persistence, recurrence, and progression of this lesion.
3.2 Special Site Nevi and Other Atypical Proliferations of Acral Skin

For many years it has been recognized that nevi on acral skin may be different from those on other sites, and that they may be difficult to distinguish from acral melanomas (1,2). Although this term refers to nevi on the skin of the palms and soles with its thick stratum corneum, similar lesions have been described in skin from the ankle, suggesting that the distal location could be an important element in the prevalence of these lesions (3). These ankle nevi exhibited moderate to severe architectural atypia in relation to histologic features including circumscription, symmetry, cohesiveness of nests, suprabasal melanocytes, confluence, single cell proliferation, nuclear hyperchromatism, size, and nucleoli features. In an earlier analysis of 158 acral pigmented lesions, including nevi and melanomas diagnosed over a 3-year period, pagetoid spread of melanocytes, often minimal, was found in about a quarter of the lesions. However, the nevi did not demonstrate the same extent of pagetoid spread, cellular atypia, inflammation, and asymmetry as was found in the malignant tumors (4). In another study of 165 plantar nevi, 36 of the nevi that had distinctive histopathological features were grouped as a special entity designated acral-lentiginous nevus. These nevi were distinguished from other acral nevi by elongation of rete ridges, continuous proliferation of melanocytes at the dermal–epidermal junction, presence of single scattered melanocytes or small clusters within the upper epidermis, poor or absent lateral circumscription, melanocytes with abundant pale cytoplasm and round to oval sometimes hyperchromatic nuclei and prominent nucleoli. The histopathologic criteria to distinguish these nevi from melanoma were lack of pagetoid lateral spread, absence of mitotic activity in the deep dermal component, and evidence of dermal nevocytic differentiation. These lesions were considered to be the benign counterpart of acral-lentiginous melanoma (5).

In terms of the etiologic/genomic/CSD classification of melanocytic lesions, acral nevi are examples of “no CSD” melanocytic proliferations.

Based on these descriptions, it is clear that there are examples of acral nevi that are difficult to distinguish from subtle examples of acral melanoma, and accordingly these lesions have been included in the concept of “nevi of special sites” (6,7), which are lesions from particular special locations that tend to present difficulty in distinction from melanoma. Clinicopathologic correlation can be of assistance, when clinical features of melanoma may be used to support a diagnosis whose histologic features are ambiguous. However, a case has been reported of “atypical melanosis of the foot” that was characterized by irregular borders and variegated pigmentation closely mimicking those of acral-lentiginous melanoma in situ. Despite the clinical atypia, the histologic findings revealed only focal, slight melanocytic hyperplasia with minimal cytologic atypia (8). This suggests again that there must be examples of lesions that cannot be interpreted with certainty, particularly when efforts are made for early diagnosis of melanoma.
In more recent times, epiluminescence microscopy, also known as dermoscopy, can be of assistance in selecting lesions for biopsy. An important distinguishing feature by dermoscopy is the distribution of pigment between furrows and ridges. If pigment is found predominantly in the furrows the lesion is more likely to be benign and if it is present predominantly on the ridges, malignancy is favored (3, 9). Although obviously useful in selecting lesions for biopsy, these criteria are not often used in establishing the specific diagnosis for which the gold standard remains the histopathology. These criteria are, of course, paralleled by histologic findings, and it has been recently shown that if melanin granules in the stratum corneum are detected as melanin columns regularly distributed under the surface furrows, the lesion is more likely to be a benign acral nevus (10).

In another study, atypical features commonly seen in benign nevi from acral sites in children included architectural atypia in the form of either lentiginous proliferation or confluence of junctional nests. In 68% of cases there was single cell infiltration of the epidermis. Atypical size, shape, and location of the junctional nests were present in 53%. Mild cytologic atypia was common (11). This finding, along with the age distribution of acral melanoma, which is weighted to a much older population, suggests that the diagnosis of acral melanoma in situ should be made with great caution if at all in the pediatric age group.

It has been suggested that acral-lentiginous nevi might represent precursors of acral-lentiginous melanoma, which would suggest that there must be overlapping lesions between the two entities. However, acral nevi do not express abnormalities in hotspots frequently associated with point mutations of the oncogene KIT in acral melanomas (12). The finding of a dermal nevus in association with acral melanoma is uncommon, but has been reported (13). Therefore, a possible preexisting nevus (junctional, dermal, or compound) needs to be distinguished from a possible nevoid vertical growth phase. In a case-control study in Japan, the total number of nevi was related to melanoma risk and was found to be a risk factor for the development of nonacral melanoma, but acquired nevi on soles, palms, and nail apparatus were not a risk factor for acral melanoma in the Japanese population (14), a finding that would suggest that acral nevi share more etiopathogenetic features with common nevi than with acral melanomas.

Based on this review of the literature and also on personal experience, it is clear that there are many instances where it may be difficult to distinguish between an acral “special site” nevus and an evolving or early established melanoma in situ. As a rule of thumb, it is apparent from the above literature and from experience that size is an important criterion in making the distinction, and therefore whenever possible, lesions should be completely excised with clear borders of normal tissue so that their size and circumscription can be evaluated. Conversely, when a junctional or in situ proliferation extends to the borders of the biopsy specimen, uncertainty is increased and clinicopathologic correlation is essential. In my opinion, it is appropriate in many of these cases to use a descriptive term such as “intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPUS)” or, if there is a dermal nevoid component of uncertain significance, the lesion can be described as a “melanocytic tumor of uncertain significance (MELTUMP)” (6). These terms, of course, do not represent diagnoses but represent a descriptive expression of uncertainty that is engendered by conflicting or inadequate criteria for making a confident distinction. The differential diagnosis should be expressed in a histopathology report, and can be used as a guide in planning therapy.
References
3.2.1

Acral-Lentiginous Nevus Versus Acral-Lentiginous Melanoma

In Situ

**CLINICAL INFORMATION**

Pigmented lesion of the right middle toe, in a 32-year-old woman.

**REASON FOR CONSULTATION**

Atypical melanocytic lesion. Specimen will be sent for consultation.

**FIGURE 3.2.1.1** An excision biopsy containing a poorly circumscribed proliferation of nevoid to epithelioid melanocytes arranged as single cells and a few nests along the dermal–epidermal junction. The specimen margins are not involved.

**FIGURE 3.2.1.2** One periphery of the lesion demonstrating the poor circumscription with the last cells being single cells, becoming attenuated at the periphery of the lesion and blending with the background normal skin.
DESCRIPTION

Sections show a biopsy of acral skin, containing an apparently small but rather ill-defined lesion, measuring about 2 mm in diameter on the slide. It is comprised of nevoid to small epithelioid melanocytes arranged in nests and as single cells, predominantly near the dermal–epidermal junction. In addition, there are some single cells that extend upward into the epidermis in a relatively well-developed pagetoid scatter pattern, focally at least to the stratum granulosum. Cytologic atypia is minimal or mild, with a few cells having small nucleoli. Taken together, these changes are consistent in my opinion with a junctional nevus of acral skin, a so-called “special site” in which pagetoid scatter of nevus cells is not uncommonly observed, although not usually to this degree. In summary, I would interpret this lesion as follows:
3.2.1

**DIAGNOSIS**

Skin, right toe: Junctional nevus, acral type, apparently completely excised, see Description and Comment.

**COMMENT**

I see no compelling evidence of malignancy in this lesion. However, if this were somehow a biopsy of a larger lesion, I would recommend complete excision of it primarily to rule out additional pathology.

**OVERALL COMMENT**

Clinicopathologic correlation with lesional morphology and especially with the lesion’s size, and knowing that the biopsy is representative of the entire lesion, are in my opinion of great importance in assessing acral lesions. In this case, the lesion appears to be completely excised with a clear margin of normal tissue indicating that it is small, and in the absence of compelling indicators of malignancy these changes are consistent with a benign “special site nevus” of acral type. In general, like all or most special site nevi and acral nevi with atypical features in particular, complete local excision is appropriate management, if only to rule out the possibility of additional pathology that has not been included in the biopsy specimen (MPATH DX Category 2).
3.2.2

Acral-Lentiginous Nevus Versus Acral-Lentiginous Melanoma

CLINICAL INFORMATION
A pigmented lesion of the right plantar foot in a 25-year-old woman, rule out melanoma.

REASON FOR CONSULTATION
Atypical compound melanocytic proliferation. Case will be sent in consultation

FIGURE 3.2.2.1

FIGURE 3.2.2

FIGURES 3.2.2.1 and 3.2.2.2 Scanning magnification profiles showing a broad, predominantly junctional proliferation in acral skin.
3.2.2

**FIGURE 3.2.2.3** There are single and nested melanocytes arranged mainly near the dermal–epidermal junction. Single cells predominate in some areas, without extensive pagetoid scatter. The pigment columns in the stratum corneum are not well defined but perhaps seem to be present under furrows.

**FIGURE 3.2.2.4** Focally there is bridging between adjacent rete; however, this is not a general characteristic of the lesion.

**FIGURE 3.2.2.5** There is moderate cytologic atypia of the junctional and dermal components. There is no evidence of tumorigenic proliferation or mitotic activity in the dermis.

**FIGURE 3.2.2.6** Changes in the epidermis extend close or to a peripheral specimen margin.
DESCRIPTION

These sections show a rather broad, asymmetric, moderately to focally more highly cellular superficial melanocytic proliferation in acral skin, comprised in its junctional component of nested and single melanocytes arranged mainly near the dermal–epidermal junction. There is, however, pagetoid scatter of single cells into the epidermis and to the stratum corneum in multiple foci across the lesion. These changes may, of course, be seen in acral nevi; however, this lesion is not especially symmetrical and appears to be quite broad, extending close or to both margins of a biopsy specimen. It will be of importance to know whether this specimen represents an attempted complete excision of a smaller lesion or incisional biopsy of a larger lesion. In any event, there is a dermal component confined to the papillary dermis and impinging on the upper reticular dermis. It is comprised of nevoid melanocytes, arranged in a mostly nested pattern. Many of them have small nucleoli and maturation appears to be somewhat incomplete. However, there is no evidence of tumorigenic proliferation or mitotic activity in this lesion. Although I would favor that this lesion represents an atypical “special site nevus” of the acral type, I am concerned about the possibility of a more significant lesion. I would therefore interpret this material descriptively as follows:

DIAGNOSIS

Skin, left plantar foot: Superficial atypical melanocytic proliferation of uncertain significance, favor an atypical “special site nevus” of acral type, extending to specimen margins, see Description and Comment.

COMMENT

As noted above, I cannot entirely rule out the possibility of an acral melanoma in this unusual lesion. If interpreted as a melanoma this would be a very low-risk lesion, nonulcerated, with tumorigenic but nonmitotic vertical growth phase, Clark’s level III, greatest Breslow thickness approximately 0.4 mm, without radial growth phase regression and without vascular, lymphatic, or neural invasion. The major concern would be for continued local persistence, recurrence, and possible future progression of the lesion if it is melanoma rather than a nevus. Clinicopathologic correlation may be of assistance; for example, if this is an attempted complete excision of a smaller lesion one would be less concerned than if there was abundant residual lesion in place. In addition, one would be more concerned if there was a history of dynamic growth or change and less concerned if this was a stable long-standing or even congenital lesion. I would also consider doing HMB 45, Ki-67, and p16 stains to assess the maturation and proliferative capacity of lesional cells in the epidermis and in the dermis. If these are reassuring, one would be more certain of the diagnosis of an acral nevus. Irrespective of these concerns, I would recommend serious consideration of an additional procedure to be sure this lesion has been completely removed with a margin of normal skin around the scar of this procedure and any residual lesion (MPATH DX Category 2 or 3). I would be interested in any follow-up findings from an additional procedure should this occur in the future.

OVERALL COMMENT

As with other acral lesions, it is important to consider the size and clinical appearance of the lesion in ruling out melanoma. This patient is rather young for more serious consideration of a diagnosis of acral melanoma. Photographic clinicopathologic correlation might be helpful but can be misleading.
3.2.3

Acral Nevus Versus Dysplastic Nevus Versus Melanoma

**Clinical Information**
A clinically atypical nevus from the left plantar surface of a 55-year-old woman.

**Reason for Consultation**
The clinicians have asked for a second opinion. I have interpreted this lesion as an atypical acral compound melanocytic lesion favoring an acral dysplastic compound melanocytic nevus, see text. In view of the atypical features, a modest wider excision may be prudent.

**Figure 3.2.3.1** A moderately cellular predominantly nested proliferation in the epidermis, with a clear margin of normal tissue on each side.

**Figures 3.2.3.2 and 3.2.3.3** In addition to the nests there are single cells around the tips and sides of elongated rete ridges.
3.2.3 Case 3: Acral Nevus Versus Dysplastic Nevus Versus Melanoma

**DESCRIPTION**

These sections show a biopsy of acral skin, containing a small but moderately to highly cellular proliferation of nevoid to epithelioid melanocytes, arranged with nests predominating along the dermal–epidermal junction. There are some bridging nests between adjacent elongated rete ridges. In the dermis there is concentric lamellar fibroplasia and a patchy lymphocytic infiltrate, and there is a focal dermal component that shows only slight, if any evidence of maturation compared to the junctional component; however, there is no high-grade uniform atypia or mitotic activity. Cytologically, the cells in the dermis and epidermis might be described as mildly to moderately atypical with prominent nucleoli. There is patchy scatter of similar lesional cells without marked atypia into the epidermis across the lesion. This change, of course, can be seen in acral nevi, representing a so-called “special site nevus” phenomenon. The other features, in my opinion, are insufficient for diagnosis of melanoma. One might consider melanocytic dysplasia; however, this is not usually seen (or at least recognized) in acral skin. Importantly, the lesion appears to be small and completely contained within the biopsy specimen. In summary, I believe these features are consistent with a special site nevus of the acral type and would characterize it as follows:

**DIAGNOSIS**

Skin, left plantar foot: Compound nevus with atypical features consistent with a special site nevus of the acral type, completely excised, see Description and Comment.

**FIGURE 3.2.3.4** A small group of lesional cells similar to those in the epidermis is present in the superficial dermis. There is no tumorigenic proliferation or mitotic activity.

**FIGURE 3.2.3.5** Melan-A staining demonstrates the poor circumscription characteristic of these acral junctional nevi, and also demonstrates scattered suprabasal melanocytes.
3.2.3

**COMMENT**

Although I do not believe this lesion is a melanoma, there is some overlap with a moderately to severely (because of the architectural features) dysplastic nevus. For this reason I would recommend consideration of this patient’s other melanoma risk factors and especially if she should have other clinically atypical nevi and/or a family or personal history of melanoma, additional evaluation and possible surveillance of her skin may be appropriate.

**OVERALL COMMENT**

In general, we do not recognize dysplastic nevi on acral skin; however, this lesion has some overlapping features, and it may be judicious to consider this patient’s general melanoma risk factors and nevus pattern. In all likelihood, this is an isolated phenomenon, consistent with a benign special site acral nevus. This lesion is completely excised; however, if it were present on the margins I would recommend an additional procedure to be sure the lesion has been completely evaluated histologically (MPATH DX Category 2).
3.2.4

Acral Versus Spitz Versus Dysplastic Nevus

**Clinical Information**
Five-year-old boy with lesion on left fifth toe, developed and has been persistent for 1 year.

**Reason for Consultation**
Is there significant atypia?

**Figure 3.2.4.1** A broad, rather highly cellular proliferation of pigmented melanocytes in acral skin.

**Figure 3.2.4.2** Many of the lesional cells are spindled and arranged in nests with prominent clefting artifact with adjacent keratinocytes. There are also single cells with pagetoid scatter into the epidermis.

**Figure 3.2.4.3** Most of the lesional cells contain abundant pigment. There is prominent pagetoid scatter of single cells into the epidermis.
3.2.4

DESCRIPTION

These sections show a biopsy of acral skin containing a lesion characterized by a moderately cellular proliferation of nevoid to dendritic cells arranged in nests and as single cells near the dermal–epidermal junction. Many single cells extend up into the epidermis in a pattern of pagetoid scatter, as may be seen in acral nevi. Relatively small size of this lesion and the lack of severe cytologic atypia or mitotic activity are reassuring factors. There is some nuclear enlargement and variability, and the presence of large spindle cells within the junctional component raises a question of a Spitz nevus/tumor or a pigmented spindle cell nevus. In any event, I believe that this lesion is benign and I would characterize it as follows:

DIAGNOSIS

Skin, left fifth toe: Junctional nevus, with Spitzoid features, and features of acral special site nevi, completely excised, see Description and Comment.

COMMENT

Assuming that this lesion is excised clinically, I do not believe any additional therapy or special follow-up is indicated.
We have seen a number of Spitzoid lesions in acral skin, which have caused difficulty in distinction from melanoma, especially in older age groups. This lesion has many features of a pigmented spindle cell nevus, which is most likely closely related to Spitz nevi/tumors. Acral-lentiginous melanoma is not a serious consideration in this age group. Although perhaps tempered by the youthful age of the patient, one would ordinarily consider complete local excision of a lesion of this sort if it were present on the margin (MPATH DX Category 2).
3.2.5

Acral Nevus Versus Lentigo, Atypical

CLINICAL INFORMATION
A 3 mm pigmented lesion on the heel of an 11-year-old boy, with a family history of melanoma in his father and uncle.

REASON FOR CONSULTATION
Is there any reason for concern about this lesion?

**FIGURE 3.2.5.1** A broad, rather ill-defined lesion in acral skin.

**FIGURE 3.2.5.2** Melan-A staining demonstrates increased numbers of single cells along the dermal–epidermal junction with a few cells rising up into the epidermis in a pagetoid scatter pattern.
**DESCRIPTION**

These sections show an excision biopsy of a relatively small lesion measuring about 2 mm in diameter on the slide. It is comprised of nevoid to small epithelioid melanocytes, arranged singly and in nests with single cells predominating, predominantly near the dermal–epidermal junction. A few cells rise slightly above the junction, and there is also pigment transport into the stratum corneum. A few scattered cells have somewhat enlarged, irregular but not especially hyperchromatic nuclei. Mitotic figures are rare or absent. I believe this lesion fits reasonably well within the parameters of acral junctional nevi, especially in a child of this age and I would interpret it as follows:
Nevi of acral skin constitute a reasonably well-characterized example of the phenomenon of “nevi of special sites.” These lesions are considered to be benign. The differential diagnosis could include a junctional nevus with mild to moderate dysplasia; however, characteristic architectural patterns are not observed. Given the family history of melanoma, it will, of course, be appropriate to evaluate this child’s other melanoma risk factors as he matures, and if he should develop other clinically atypical nevi, or if he has sun sensitive skin, consideration of surveillance may be appropriate. There is a clear margin of normal tissue of at least 1 mm on each side of the lesion in the sections available for study.

**OVERALL COMMENT**

There is a suggestion from one study that acral nevi may be more common in members of melanoma-prone families (15). However acral nevi, per se, have not been associated with increased risk for melanoma including acral melanoma. This lesion is quite innocuous especially in this age group, and a reexcision procedure might not be necessary, even if margins were involved, as long as the biopsy represented a substantially complete excision of the clinically benign lesion (MPATH DX Category 1). Given the family history of melanoma, the family would likely be more comfortable with a complete excision procedure (Category 2) as in fact has been done in this case.
3.2.6

Acral Nevus Versus Lentigo

**Clinical Information**
A pigmented patch of the left thumb in an 11-year-old girl with a family history of melanoma and multiple clinically atypical pigmented lesions elsewhere on her skin.

**Reason for Consultation**
Is there significant atypia in this lesion?

*Figure 3.2.6.1* An excision specimen of acral skin.

*Figure 3.2.6.2* and *Figure 3.2.6.3* There is an increased number of single and ill-defined nested melanocytes along the dermal–epidermal junction. The lesion is quite subtle.
Section 3.2: Special Site Nevi and Other Atypical Proliferations of Acral Skin

3.2.6

**DESCRIPTION**
Sections show a biopsy of acral skin, containing a small lesion less than 2 mm in diameter on the slide comprised of nevoid melanocytes arranged mainly near the junction. As may be seen in so-called “special site” acral nevi, especially in children, there is some tendency to scatter of single cells into the epidermis. There is no high-grade atypia, continuous basal proliferation, mitotic activity, or other evidence of malignancy.

**FIGURE 3.2.6.4** There is only slight nuclear size and shape variation. A few cells rise above the junction.

**FIGURE 3.2.6.5** The lesion is completely excised with clear margins.

**DIAGNOSIS**
Skin, left thumb: Junctional nevus, acral type, excised.

**COMMENT**
This lesion has minimal nesting and could be considered to overlap with a simple lentigo.

**OVERALL COMMENT**
There is slight suprabasal scatter as may be seen in acral nevi. This lesion could be simply observed (MPATH DX Category 1), or excised as in this case with close but clear margins. There is likely no relationship with the family history of melanoma.
3.2.7

Atypical Nevus Versus Melanoma

CLINICAL INFORMATION

Thirty-six-year-old female, left foot plantar. Patient has a 1.5 \times 1.0 \text{ cm} lesion for 7 years and clinically “rule out melanoma.”

REASON FOR CONSULTATION

Our differential diagnosis: melanoma in situ (MIS) versus atypical junctional nevus.

FIGURE 3.2.7.1 A punch biopsy of skin that contains a junctional proliferation of nevoid to epithelioid melanocytes. There is a deceptive impression that the lesion is small, and completely excised; however, the distribution of cells along the junction is patchy, and clinically the lesion measured 1.5 cm in greatest dimension.

FIGURES 3.2.7.2 and 3.2.7.3 Much of the lesion is comprised of single cells located near the dermal–epidermal junction, with a few cells rising slightly above the junction. The nuclei are small without irregularity or hyperchromatism.
3.2.7

**DESCRIPTION**

These sections show a punch biopsy of acral skin, containing a moderately cellular proliferation of nevoid to epithelioid and dendritic melanocytes, arranged singly and in nests, predominantly near the dermal–epidermal junction. The proliferation is mainly confined to the tips and sides of elongated rete ridges without extensive continuous proliferation between the rete. In addition to the junctional proliferation, there is pagetoid scatter of lesional cells into the epidermis and into the stratum corneum. Cytologically, the lesional cells have moderately enlarged, somewhat irregular nuclei, some with relatively prominent nucleoli. Taken in conjunction with the clinical history of a 1.5 × 1.0 cm lesion present for 7 years, these findings are quite concerning for melanoma, which in this biopsy would be in situ. Because some of these features overlap with those of acral nevi, however, I do not believe these changes are independently diagnostic of melanoma and would characterize this specimen descriptively as follows:

**DIAGNOSIS**

Skin, left foot plantar: Intraepidermal atypical melanocytic proliferation (IAMPUS), acral junctional nevus versus melanoma in situ, see Description and Comment.

**COMMENT**

Although I am concerned about the possibility of melanoma in situ of the acral-lentiginous type, I believe that these changes could also be consistent with an atypical “special site nevus” of the acral type. If it can be done without severely compromising function, complete excision of this lesion would be the most appropriate course to take, I believe. A more
definitive interpretation may well be available when the complete lesion is available for inspection. Alternatively, possibly additional biopsies could be done to sample a greater extent of the lesion and rule out invasion. In any event, if the lesion is not excised, I would recommend careful clinical follow-up with photographic documentation and if the lesion should show any dynamic changes (and indeed, if these have been documented in the past), I would recommend complete excision of it (MPATH DX Category 2).

**OVERALL COMMENT**

In my opinion, lesional size is a significant criterion in establishing a diagnosis of melanoma in situ, acral-lentiginous type, and clear specimen margins in a small lesion that lacks severe uniform atypia, mitotic activity, and other compelling attributes, are very helpful in ruling out melanoma.
4.0 Vulvar Melanomas, Nevi, and Lentigines

4.1 Vulvar Melanoma
  4.1.1 Malignant Melanoma Versus Inflamed Atypical Nevus
  4.1.2 Malignant Melanoma Versus Atypical Genital Nevus
  4.1.3 Malignant Melanoma Versus Atypical Nevus
  4.1.4 Vaginal Melanoma Versus Atypical Nevus
  4.1.5 Vulvar Melanoma Versus Atypical Nevus

4.2 Special Site Nevi and Other Atypical Proliferations of Genital Skin
  4.2.1 Compound Nevus Versus Dysplastic Nevus
  4.2.2 Dysplastic Nevus Versus Special Site Nevus
  4.2.3 Vulvar Nevi Versus Melanoma
  4.2.4 Atypical Nevus Versus Melanoma
  4.2.5 Spindle Cell Nevus Versus Melanoma
  4.2.6 Vulvar Nevi Versus Dysplastic Nevus Versus Melanoma
Melanoma occurs on mucosal surfaces of various sites, including the sinonasal passages of the head and neck, the oral cavity, perianal skin, and mucosae, and very rarely in mucosal surfaces of visceral organs (1). One of the commonest mucosal sites is the vulva, which is a structure that has both mucosal and cutaneous surfaces. In either case, this may be classified as a “no CSD” location. Melanocytic nevi and lentigines also occur in these sites (2–4). The etiology of these melanocytic proliferations in mucosal sites is not understood.
Vulvar melanoma has been said to be the second most common vulvar malignancy and certainly represents a significant women’s health issue (5). In a review of 21 cases, a family history of cutaneous melanoma was present in 15%. The mean Breslow depth was 2.8 mm. Sentinel node biopsy was positive in two of 10 patients. One patient had a germline mutation in the MC1R gene. It was considered that vulvar and cutaneous melanoma behave similarly despite their different pathogenesis (5). In another study of 51 patients, the median age was 54 and 39% of the patients presented with a mass. Sixty five percent of the lesions were on the mucosa and 21% on the epidermal surfaces of the vulva. Despite complete surgical resection, 63% of the patients’ lesions recurred. Median survival was 41 months. As with cutaneous melanoma the AJCC classification, Breslow thickness and Clark’s levels were the major predictors of overall survival. It was considered that surgical techniques do not seem to alter the prognosis. In another review of surgical outcomes from five medical centers, surgical radicality was associated with significant morbidity but did not impact recurrence rates or survival. Breslow thickness was associated with recurrence but not survival. The AJCC staging criteria are predictive of overall survival (6,7). Although most patients with mucosal melanoma of the genital tract are postmenopausal, there is a wide range of age, from 10 to 99 years in one recent review (7).

Clinical features of mucosal melanomas in general and vulvar melanoma in particular are similar to those of melanomas elsewhere. There is often a relatively indolent and asymptomatic period in which the lesion spreads within the epidermis to produce a radial growth phase lesion, which is typically characterized by the ABCD (asymmetry, border irregularity, color variegation, diameter > 4 mm) characteristics of radial growth phase lesions of melanomas elsewhere. Tumorigenic vertical growth phase may supervene, in which case there is development of a nodular component that may be amelanotic and pink or may be partially or heavily pigmented. There are also examples of pure vertical growth phase melanomas similar to nodular melanomas of the skin that lack an adjacent in situ superficially invasive radial growth phase component. Some of these lesions may have overgrown a preexisting smaller radial growth phase/in situ component. Dermoscopic features of vulvar pigmented lesions have recently been described (8–10). In a series of 68 consecutive biopsied cases of vulvar pigmented lesions, benign melanosis and postinflammatory hyperpigmentation were the most frequent diagnoses (63% of cases). Nevi accounted for 24% and melanomas for 7% of the cases. The dermoscopic criteria applicable to other cutaneous nevi and melanomas, in general, applied. The epithelial pigmentations (lentigines, vulvar melanosis, and postinflammatory hyperpigmentation) tended to show a “parallel pattern.” It was not possible by dermoscopy to distinguish among these conditions (10).

Histologically, it has long been known that many mucosal melanomas are associated with lentiginous proliferation in the epithelium adjacent to a
section 4.1: Vulvar melanoma

Tumorigenic vertical growth phase, giving rise to the term “mucosal-lentiginous melanoma” (11,12). This pattern of a lentiginous in situ component may be seen in all of the mucosal sites and is characterized by predominance of single cells, continuous basal “lentiginous” proliferation, and some tendency to pagetoid scatter, which is diagnostically helpful. Many of these lesions are heavily pigmented, but some are oligomelanotic or amelanotic. The tumorigenic vertical growth phase, when present, may resemble that in other melanomas, especially the lentiginous melanomas. As in other lentiginous melanomas, a desmoplastic vertical growth phase may occur and there may also be neurotropism (13). In addition, there are tumorigenic melanomas that develop without a preexisting radial growth phase, analogous to nodular melanomas of the skin. In our experience, there are also melanomas of the vulva that more closely resemble pagetoid (i.e., superficial spreading) rather than lentiginous melanomas of other skin surfaces. These tend to be located in the vulvar skin rather than mucous membrane, to have extensive pagetoid scatter, prominent nesting, and prominent pigmentation and to be comprised of large epithelioid cells. Some of them may be associated with preexisting nevi, in some cases dysplastic nevi. Therefore, there may be two pathways to progression toward melanoma in vulvar skin, a nevogenic/pagetoid pathway and a lentiginous pathway. In neither case does ultraviolet (UV) exposure seem to play a prominent role.

Vulvar melanoma may be associated with benign or atypical preexisting lesions that have been described as “melanocytic dysplasia of various degrees” (14) or as “atypical melanocytic hyperplasia adjacent to the primary melanoma” (7). In our experience, dysplastic nevi and other nevi may occur on the skin of the vulva, and these need to be distinguished from atypical “special site” nevi of vulvar skin, to be discussed in the next section. However, the lesions that are associated with vulvar melanomas often appear to be lentiginous proliferations that fit better into the category of mucosal lentigines rather than mucosal nevi, and have been described as “genital lentiginosis” (15). It can be very difficult to make clear distinctions between mucosal lentigines with atypia and evolving or early established melanoma in situ. These issues are discussed in this section and the next section.

In terms of the etiology/site-related/genetic classification of melanomas, vulvar and mucosal genital melanomas are not, of course, associated with chronic solar damage, and are therefore “no CSD” melanomas. In a study of the relationship between sun exposure and vulvar melanoma, it was found that the incidence rates of cutaneous melanoma have increased with time until recently, while those of vulvar melanoma had either decreased or remained constant in several populations studied. Comparison of latitudinal trends showed that while cutaneous melanomas increased with increasing sun exposure, the ratio of vulvar melanomas to cutaneous melanomas decreased. The findings supported the presumption that vulvar melanomas are not generated by UV radiation, and also the possibility that solar UV radiation perhaps via its role in vitamin D photosynthesis might have a protective effect against vulvar melanoma (16).

In a recent study of mucosal melanomas, including five vulvar melanomas, by whole genome sequencing, recurrent mutations were found in several genes including KIT, PTEN, TPR, and TTN (17). Somatic mutation rates were considerably lower than those that occur in sun-exposed cutaneous melanoma but comparable to the rate seen in cancers not associated with exposure to known mutagens. The mutation signatures were not those of UV light or tobacco smoke–induced DNA damage. The findings suggest that the mechanisms involved in the development of mucosal melanomas differ from those in usual cutaneous melanomas (17).
References


4.1.1

Malignant Melanoma Versus Inflamed Atypical Nevus

**Clinical Information**
3 cm variably pigmented lesion of the right vulva in a 32-year-old female, which had been previously biopsied at another hospital.

**Reason for Consultation**
Although malignant melanoma is favored here, this pigmented lesion demonstrates some unusual features, which appear to be present in association with a preexisting nevus, making it unclear as to whether invasion is present or not. Evaluation is also somewhat hindered by a marked lymphoplasmacytic infiltrate and abundant pigment incontinence. Because of these difficulties the case will be sent for further evaluation.

**Description**
On receipt in your laboratory, the specimen was consistent with a partial vulva with a flat poorly defined variably pigmented lesion present on the surface of the specimen measuring 2.3 cm in greatest dimension. Microscopically, the sections show an extensive proliferation of uniformly atypical epithelioid and somewhat spindled melanocytes in the epidermis, arranged in nests that tend to become confluent and as single cells that are present in a continuous pattern along the dermal–epidermal junction, diagnostic of melanoma in situ. In addition to the more obviously atypical proliferation, adjacent to it there is an increased number of slightly enlarged melanocytes arranged as single cells near the dermal–epidermal junction, resulting in a very ill-defined border to the lesion. In the dermis, there is a bandlike lymphocytic infiltrate. I agree that it can be difficult to assess invasion because of the presence of epithelial hyperplasia extending down into the dermis; however, I believe there are several areas where there is frank invasion of the dermis by uniformly atypical cells that I cannot interpret as nevic because of their atypia,

**Figure 4.1.1.1** A broad, asymmetrical, and highly cellular proliferation.
4.1.1.3

The lesional cells are arranged in nests piling upon one another to form an “accretive” vertical growth phase.

4.1.1.4

Closer to the surface of the image in Figure 4.1.1.3, there is confluence of uniformly atypical cells. Mitotic figures (not shown) were also seen in this area.

4.1.1.5

In another area, there is pagetoid scatter of single cells and nests of atypical melanocytes, with similar smaller clusters of cells in the dermis in relation to a bandlike lymphoplasmacytic infiltrate.

failure of complete maturation, focal mitotic activity, and multifocality across the lesion. Thickness is also somewhat difficult to interpret because of tangential sectioning in some cases, and in particular I would ignore an area on which I believe represents tangentially sectioned tumor related to
of continuity of the surface with an inflammatory host reaction. I doubt that this is related entirely to a prior biopsy because I do not believe that such a biopsy would have been so superficial. However, I do not clearly see evidence of a prior biopsy elsewhere in the specimen. Nevertheless I think it is best to regard this lesion as ulcerated. I would therefore characterize this tumor as follows:

**COMMENT**

Although malignant melanoma is very rare in the vulva in premenopausal women, there is no doubt about the diagnosis in this case and this lesion is clearly not an atypical nevus of the genital type, based on the severe atypia, confluence of the epidermal component, extension of the epidermal component beyond the dermal component, and failure of maturation as well as mitotic activity in the dermal component. Excision of the frank melanoma appears to be complete in the multiple section planes available for study; however, subtle atypical melanocytic hyperplasia extends close to a surface that may not be a true inked margin in one designated block, and because these lesions may sometimes present as “field effects,” careful continuing follow-up for possible local persistence/recurrence is, of course, recommended. One would also consider sentinel lymph node sampling for a lesion with these attributes, if not contradicted for any other reasons (MPATH DX Category 5).
CASE 1: MALIGNANT MELANOMA VERSUS INFLAMED ATYPICAL NEVUS

OVERALL COMMENT

Malignant melanoma of the vulva is very rare in this age group, but we have seen a fatal case in a 19-year-old. Nevertheless, the diagnosis of melanoma should be made with great circumspection in premenopausal women, as atypical “special site” nevi of the vulva can exhibit marked atypia as illustrated in section (4.2).
4.1.2

Malignant Melanoma Versus Atypical Genital Nevus

**Clinical Information**
A lesion from the vulva in a 20-year-old woman.

**Reason for Consultation**
Please review this unusual material.

**Figure 4.1.2.1** An excision biopsy of a broad lesion with an asymmetrical profile, in vulvar skin.

**Figure 4.1.2.2** To the left of the image, there are discrete nests arranged mainly near the tips and sides of elongated rete ridges, in the pattern of a junctional dysplastic nevus.

**Figure 4.1.2.3**
These sections show a moderately to highly cellular, asymmetrical, and poorly circumscribed lesion comprised of a uniformly atypical population of large epithelioid melanocytes, having relatively abundant cytoplasm with sparse finely divided melanin pigment. Lesional cells tend to have quite large, somewhat irregular and often hyperchromatic nuclei with prominent nucleoli. Although one might consider a Spitz nevus/tumor, the cytology is not characteristic, there is variation in size and shape of cells from side to side, and there are no Kamino bodies at the junction. There is also a dermal component comprised of cells similar to those in the epidermis, which shows little or no evidence of maturation and extends into the reticular dermis.

In summary, despite the youthful age of this patient, I would agree with the diagnosis of melanoma, which I would consider to be invasive and would characterize as follows:

**FIGURES 4.1.2.3 and 4.1.2.4** Toward the center of the lesion, there are nests that vary in size, shape, and distribution in the epidermis, and there are nests and fascicles of uniformly atypical epithelioid cells in the dermis.

**FIGURE 4.1.2.4** Irregularly distributed nests and single cells with low-level pagetoid scatter and irregular hyperplasia in the epidermis.

**FIGURE 4.1.2.5** Toward the center of the lesion, there are nests that vary in size, shape, and distribution in the epidermis, and there are nests and fascicles of uniformly atypical epithelioid cells in the dermis.

**FIGURE 4.1.2.6** Another area of invasion of the dermis by uniformly atypical epithelioid melanocytes.
COMMENT

Adjacent to the melanoma there is evidence of a junctional dysplastic nevus comprised of predominantly epithelioid cells with nuclei that are noticeably smaller than those of the melanoma component of the lesion. Deep to this region there is a collection of cells in the dermis and I believe this represents a remnant of a congenital pattern nevus component. The dermal mitotic rate is zero in this material, tumor-infiltrating lymphocytes are very sparse, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. Although it is invasive, the prognosis for this lesion should be very good in terms of any potential for metastasis because it is thin and nonmitogenic. I believe this lesion would have potential for persistence, recurrence, and progression if not adequately removed. Changes in the epidermis extend close or to specimen margins and I would, of course, recommend definitive therapy for this lesion based on the above diagnosis (MPATH DX Category 4).

OVERALL COMMENT

This is a very difficult diagnosis. The melanoma itself has characteristics of superficial spreading rather than mucosal-lentiginous melanoma, which is very rare although not nonexistent in premenopausal patients, and I would consider it most likely to have risen in a precursor nevus, perhaps explaining its occurrence in such a youthful patient. Although melanoma is rare in premenopausal women, and the diagnosis should be made with great caution, we have seen an unquestioned fatal example in a 19-year-old.
4.1.3

Malignant Melanoma Versus Atypical Nevus

CLINICAL INFORMATION
An atypical lesion of the vulva in a 59-year-old woman.

REASON FOR CONSULTATION
We believe that this lesion is a melanoma, and that the cells in the lymph node are consistent with capsular nevus.

FIGURE 4.1.3.1 A broad, highly cellular lesion with an asymmetrical profile.

FIGURE 4.1.3.2 At one periphery of the lesion there are nests of pigmented melanocytes with pagetoid scatter into the epidermis, and with a few single cells forming a poorly circumscribed border.

FIGURE 4.1.3.3
4.1.3

**FIGURE 4.1.3.4** In the center of the lesion the proliferation is highly cellular with confluence of nests and epidermal hyperplasia.

**FIGURE 4.1.3.5** In this region there is diffuse fibroplasia with a moderately brisk lymphocytic infiltrate, scattered melanophages, and clusters of invasive atypical melanocytes in the superficial dermis.

**FIGURE 4.1.3.6** In a sentinel node procedure, nevoid cells were identified in the capsule of the node.

**FIGURE 4.1.3.7** Capsular nevus cells, characterized by small nuclei without nucleoli and without mitotic activity, located in the capsule rather than in the subcapsular sinus or parenchyma of the node.
DESCRIPTION

These sections show, in the vulvar melanoma specimen, a lesion characterized by a markedly cellular proliferation of epithelioid melanocytes, present near the dermal–epidermal junction as nests and single cells and extending up into the epidermis in a prominent pagetoid scatter pattern to the stratum corneum. In the dermis, there is diffuse fibroplasia and a band-like lymphocytic infiltrate. Lesional cells protrude into the dermis associated with epithelial hyperplasia. These cells must be interpreted as invasive although possibly retaining some tenuous connection to overlying epithelium. There is also a region of fibroplasia with focal loss of lesional cells from the overlying epidermis, consistent with focal radial growth phase regression. Of interest, the appearances in this lesion are those of a superficial spreading pattern of melanoma with high nesting, scatter and pigment and with large cells, compared to the more usual mucosal-lentiginous pattern. In summary, I would interpret this lesion as follows.

Sections of the lymph nodes show collections of cells in the capsule; these stain positively with Melan-A and they have small nuclei without nucleoli and without mitotic activity. The location and the cytology are consistent with capsular nevus cells. I see no evidence of metastatic melanoma. Therefore I would interpret these findings as follows:

**DIAGNOSIS**

Skin, vulva: Malignant melanoma, superficial spreading type, nonulcerated, nontumorigenic, and nonmitogenic invasive radial growth phase only in this one section, Clark's level II, greatest Breslow thickness 1.0 mm, see Description and Comment.

Lymph node, right groin: Benign lymph node profiles with capsular nevus cells, see Description.

COMMENT

Measurement of thickness in this lesion is difficult because it is difficult to be certain that there are cells in the dermis clearly separated from the overlying epidermis, which is hyperplastic. Nevertheless, there does appear to be evidence of protrusion of cells into the dermis and therefore the deeper cells in contact with the epidermis have been measured for this microstage. Even so, the volume of invasive tumor appears to be very small in this single section available for review. There is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. There is focal evidence of radial growth phase regression. Of course, these findings should be correlated with those from any previous biopsy that has been done. This is a lesion for which sentinel node staging is a reasonable consideration (MPATH DX Category 4 or 5).

**OVERALL COMMENT**

This lesion has morphological characteristics of melanoma of the superficial spreading type, even though, of course, it is not likely to have been associated with UV exposure.
4.1.4

Vaginal Melanoma Versus Atypical Nevus

CLINICAL INFORMATION
Pigmented lesion of the vagina in a 40-year-old woman.

REASON FOR CONSULTATION
We favor a diagnosis of melanoma but wish to rule out an atypical genital nevus.

FIGURE 4.1.4.1 The biopsy specimen demonstrates a highly cellular pigmented lesion comprised of asymmetrically distributed cells.

FIGURE 4.1.4.2 There is diffuse fibroplasia, a lymphocytic infiltrate, and numerous melanophages in the stroma.

FIGURE 4.1.4.3 Continuous and nested proliferation of atypical cells in the epithelium.

FIGURE 4.1.4.4 Melan-A stain demonstrates continuous proliferation and confluent nests in the epidermis and a few cells protruding into the dermis as small clusters.
DESCRIPTION
These sections show a punch biopsy of squamous mucosa showing a markedly increased number of uniformly atypical nevoid to epithelioid melanocytes arranged in a partly continuous pattern along the basal layer, and extending into the epithelium although generally not beyond the lower third. Cytologic atypia is generally uniform, and focally severe. In the lamina propria, there is a brisk lymphocytic infiltrate with diffuse fibroplasia and melanophages, and at least a few lesional cells are also present, without tumorigenic proliferation or mitotic activity. In summary, I would agree with your interpretation of this lesion as follows:

DIAGNOSIS
Vagina: Malignant melanoma, mucosal-lentiginous type, focally invasive with nontumorigenic and nonmitogenic radial growth phase only, Clark’s level II, greatest Breslow thickness 0.32 mm in the section planes available for study (0.45 mm by report).

COMMENT
If this small biopsy is representative, this lesion is nontumorigenic and nonmitogenic, with brisk tumor-infiltrating lymphocytes, without radial growth phase regression, with no ulcer, and without microscopic satellites or vascular or lymphatic invasion. Changes extend to specimen margins, and correlation with findings from a completely excised lesion will be indicated for definitive microstaging. This lesion could be provisionally managed as MPATH DX Category 4.

OVERALL COMMENT
The degree of cytologic atypia and confluence in this lesion are beyond what could be accepted in a genital nevus and in any case these lesions have not to our knowledge been described in the vagina.
4.1.5

Vulvar Melanoma Versus Atypical Nevus

**CLINICAL INFORMATION**

Wide excision of biopsy proven vulvar melanoma in a 66-year-old woman.

**REASON FOR CONSULTATION**

Please evaluate specimen margins.

---

**FIGURE 4.1.5.1** Sections show a very broad, highly cellular proliferation in the epidermis within asymmetrically distributed cellular infiltrate in the dermis.

**FIGURE 4.1.5.2** The cells in the epidermis are arranged in nests, which tend to become confluent, and as single cells, which tend to extend into the epidermis in a pagetoid scatter pattern generally in the middle and lower thirds.

**FIGURE 4.1.5.3** In this region, there is some overlap with the architectural morphology of a dysplastic nevus. Cytologically, the lesional cells exhibit moderate to severe uniform cytologic atypia.
Sections show a very broad, highly cellular proliferation of large epithelioid and spindle melanocytes. These are arranged singly and in nests, with single cells predominating in some areas and with confluence of nests along the dermal–epidermal junction. There is pagetoid scatter of single cells into the epidermis mostly to the lower and middle thirds. In the dermis, there is diffuse fibroplasia and a patchy to focally bandlike lymphocytic infiltrate with numerous melanophages. Based on uniform cytologic atypia, the confluence of nests and the pagetoid scatter, and also taking into consideration the age of the patient, I believe these findings are diagnostic of melanoma, at least in situ.

**Diagnosis**

Skin, anterior vulva, wide excision: Malignant melanoma, mucosal-lentiginous type, at least in situ, extending close to inked resection margins, see Description and Comment.

**Comment**

There may be a few lesional cells in the stroma; however, there is certainly no evidence of tumorigenic proliferation or mitotic activity. I believe this is a lesion that could have competence for persistence, local recurrence and possible future progression if not completely excised (MPATH DX Category 4). The lesion extends within 1 mm of a closest peripheral resection margin.
4.1.5

**OVERALL COMMENT**

Although I had considered this lesion to represent a mucosal-lentiginous melanoma, it has high nesting and high pigment but low scatter, overlapping with the morphology of superficial spreading melanoma, and there is also a suggestion that it may have arisen in a dysplastic nevus, a lesion that can be seen in the vulva.
There are two major subtypes of clinically and/or histologically atypical lesions of genital skin. The most common of these are compound and junctional nevi similar to those that occur in skin of general body surfaces, occurring in the cutaneous surfaces of the vulva. Another common subgroup clinically presents as “mucosal melanotic macule,” and histologically may be characterized by lentiginous proliferation without nesting, placing it in the general category of a lentigo, or as epithelial hyperpigmentation without melanocytic proliferation without melanocytic proliferation, termed “mucosal melanosis.” In yet another group of cases, clinically atypical hyperpigmentation is associated with melanophages in the dermis or superficial mucosa, representing postinflammatory hyperpigmentation. It is not possible to distinguish clinically among these latter three conditions, even with dermoscopy (1).

A subset of nevi on genital skin falls into the general category of “special site nevi” (2). These include acral nevi, which have previously been discussed, and an ill-defined group of nevi from a variety of other special sites, to be discussed in a following section. Because genital nevi are commonly encountered as diagnostically problematical biopsies and because of the importance of vulvar melanoma in the differential diagnosis, these are discussed separately in this section.

**GENITAL LENTIGINES**

Mucosal lentigo or “genital lentiginosis” has been described in a few reports. Barnhill et al. described 10 lesions that were relatively large, multifocal, and irregular in outline and had variegated pigmentation and were regarded as clinically atypical in appearance (3). Some lesions that we have seen have closely simulated melanoma clinically. Dermoscopic features of mucosal melanosis have been described (4). The lesions studied in this report were biopsied and did not show histologic atypia despite considerable clinical atypia in some cases. Histologically, the lesions showed basal layer hyperpigmentation, slight melanocytic hyperplasia, epithelial hyperplasia, and stroma melanophages. No cytologic atypia of melanocytes was detectable in this report. However, in subsequent experience we have seen examples of these cases that have had varying degrees of melanocytic proliferation and atypia, although generally slight in degree, overlapping with the histology of evolving or early established melanoma in situ. Similar changes can also be seen in the skin adjacent to authentic melanoma in these sites. Generally speaking, excision of these lesions is recommended. Sometimes they are multifocal, making surgical clearance difficult, and in this case the lesions may be followed. Unfortunately, formal follow-up studies are not available.
These lesions are easily distinguishable from mucosal melanosis, where there is hyperpigmentation of basal keratinocytes but no melanocytic proliferation (4).

**GENITAL NEVI**

It has been recognized for many years that there is variation in the morphology of nevi among different sites on the body. One of the best characterized of these so-called “special sites” is the skin and mucous membranes of the vulva, and to a lesser extent the vagina and the perineal skin, especially in women. In the first clear description of this phenomenon, biopsies of 85 pigmented vulvar lesions from women 13 to 73 years of age were studied (5). There were 59 nevi, 16 lentigines, four melanomas, and six miscellaneous lesions. The nevi were compared to a control series of 200 nevi from the trunk of women. Three of the vulvar nevi were considered to be unusual but not dysplastic. The lesions were characterized by large junctional nests of melanocytes with variability in the size, shape, and position of the nests.

In a later study, 56 genital area melanocytic lesions were reviewed (6). Among these, there were two distinctive pathological categories. One of these was termed “atypical melanocytic nevi of the genital type” (AMNGT), while 14 were considered to be dysplastic nevi. The remaining six cases were common nevi without atypia. The atypical genital nevi were usually located on the vulva but also were seen on the perineum mons pubis, and in the axilla.

In a more recent study of 56 cases of “atypical genital nevi” rising in the lower female genital tract, the median age was 26 years (7). The lesions were characterized by a lentiginous and nested junctional component composed of prominent round or fusiform nests with retraction artifact and/or cellular dyshesion. There was cytologic atypia, which was mild in 20%, moderate in 60%, and severe in 20%. In 18% of the cases there was focal pagetoid spread. The atypical junctional proliferation was associated with a large common dermal nevus component. There was nuclear atypia of melanocytes in the superficial dermis although dermal mitoses were uncommon (7%) and all cases showed evidence of maturation. Only one case recurred in a lesion that previously had mild atypia and was present at the margins of excision. There was no further recurrence of this lesion after reexcision. It was considered that the data support the hypothesis that atypical genital nevi have a benign clinical course despite their occasionally striking cytological and architectural atypia.

In a recent review, genital nevi of special sites were characterized by the prominent, junctional proliferation of round-to-oval nests that may become confluent. Three architectural patterns were described: first, a nested pattern of large often oval nests often perpendicular or parallel to the dermal–epidermal junction; second, a dyshesive nest pattern of nearly contiguous dyshesive nests forming a band that separated the epidermis from mature dermal melanocytes; and third, a crowded pattern of ill-defined nests and single cells that were closely apposed, obscuring the dermal–epidermal junction. These lesions could also display other concerning features such as diffuse moderate to severe cytologic atypia, epithelioid cells with prominent nucleoli, focal central pagetoid spread although rarely above the granular layer, and a broad zone of superficial dermal fibrosis. An underlying population of benign appearing dermal nevus cells often formed a mushroom shape with atypical nevus cells overlying the dermal component. Reassuring features in these lesions included symmetry, well demarcated borders of the lesion, dermal maturation, and low dermal mitotic activity (8). Recent dermoscopic studies have tended to suggest that characteristics applicable to lesions of other body surfaces are helpful in selecting lesions for biopsy from vulvar surfaces (1,4,9).
In a study of mutation status of the BRAF oncogene, the common V600E mutation was found in three of seven genital nevi without atypia and three of 13 atypical genital nevi (10). This prevalence is somewhat lower than that in common cutaneous nevi but suggests that these lesions may be closely related.

These reviews and our personal experience indicate that atypical genital nevi can pose a major problem in their distinction from superficial melanoma. Although melanoma is rare in premenopausal women, we have seen unquestioned cases that have exhibited aggressive behavior including a lethal outcome. Therefore, not all superficial atypical melanocytic proliferations in the vulva can be put into the category of atypical genital nevi. In the earlier descriptions of these lesions, some emphasis was placed on the compound nature of the lesions, with the atypical junctional component being confined to the epidermis above a dermal component, which showed evidence of maturation from superficial to deep. Mitotic figures were considered to be rare or absent in these lesions. In more recent studies and usage, the concept of atypical genital nevi has been extended to include lesions with a junctional component that extends beyond the dermal component, and even to lesions that are entirely junctional. In our opinion, these lesions can be very difficult and sometimes impossible to distinguish from in situ or superficially invasive melanomas, and in such cases a descriptive diagnosis of MELTUMP or SAMPUS may be the best that can be rendered (2). Underdiagnosis leading to undertreatment could have a disastrous result, and we recommend reporting of microstaging attributes that would be appropriate if the lesion were interpreted as a melanoma, and management with the differential diagnosis taken into consideration. Although reasonable to discuss, in our opinion sentinel node staging is not necessarily standard of care in these ambiguous lesions.

References
4.2.1

**Compound Nevus Versus Dysplastic Nevus**

**Clinical Information**

Atypical pigmented lesion from the left labia of a 12-year-old girl, clinically 1.4 cm in greatest dimension.

**Reason for Consultation**

This appears to represent a compound melanocytic nevus with moderate epithelioid cytologic atypia; however, there are a few solitary melanocytes in the upper layers of the epidermis and significant disconnection of junctional melanocytes. We would greatly appreciate your opinion.

**Figure 4.2.1.1** A plaquelike lesion with irregular architectural features at scanning magnification.

**Figure 4.2.1.2**

**Figure 4.2.1.3**
CASE 1: COMPOUND NEVUS VERSUS DYSPLASTIC NEVUS

4.2.1

FIGURES 4.2.1.2–4.2.1.5 There are large and smaller nests at the junction, comprised of large cells with dyshesion artifact. There is fibroplasia and a dense lymphocytic infiltrate in the dermis. Cells similar to those in the epidermis are present in the papillary dermis and reticular dermis, and show some evidence of maturation upon descent.

FIGURE 4.2.1.4

FIGURE 4.2.1.5

DESCRIPTION

These sections show a biopsy of skin from the left labia of a 12-year-old girl. The sections show a moderately cellular proliferation of melanocytes in the epidermis and in the dermis. In the epidermis, there is a predominantly junctional proliferation of large epithelioid melanocytes with abundant cytoplasmic melanin pigment. These cells are arranged in nests that tend to vary in shape and also exhibit discohesion, as you note. There are also single cells, a few of which rise somewhat above the junction in a pattern of rather low level and patchy pagetoid scatter. There is also a dermal component, comprised in part of lesional cells similar to those in the epidermis, having relatively abundant cytoplasm and finely divided melanin pigment, which appear to be continuous with a more mature population of smaller nevoid melanocytes that extend focally to the base of the biopsy but appear to be dispersing into the reticular dermis in a “congenital pattern.” Mitotic figures are rare or absent in multiple section planes studied. A Ki-67 study demonstrates only a few cycling lesional cells in the junctional component, and essentially none in the dermal component. An HMB 45 stain is “top heavy,” indicative of maturation of the dermal component. The junctional component does not...
4.2.1

appear to extend appreciably beyond the periphery of the dermal component; however, the junctional component extends close to specimen margins and the dermal component is transected at the base. Taking these findings together, I believe that this lesion does not meet criteria for melanoma and is consistent with a so-called “special site nevus” of the vulva, which I would characterize further as follows:

**DIAGNOSIS**

Skin, left labia: Compound nevus with architectural and cytological disorder, present at specimen base and close to margins, see Description and Comment.

**COMMENT**

As noted above, I believe that this lesion fits quite well into the category of special site nevi of genital skin. These lesions have been well described over a number of years and are characterized by large cells in large nests with dyshesion in the junctional component, and by maturation of an underlying junctional component. There is usually not a substantial adjacent intraepidermal component beyond the last dermal nevus cells, the possibility that is suggested in some of the section planes in this lesion, which is an atypical feature. Because these lesions are unusual, and characterized by cytologic atypia as well as architectural disorder, I would recommend an additional surgical procedure to be sure this lesion has been completely removed with, at a minimum, a margin of normal tissue around the scar of this procedure and any residual lesion. The purpose of this reexcision is to allow for complete evaluation of this atypical lesion and also to preclude any possibility of persistence, recurrence, or progression of it in the future. The differential diagnosis for this lesion could include severe dermal and epidermal melanocytic dysplasia with a question of evolving melanoma in situ, although I do not favor this. For this reason I would recommend evaluation of this patient’s other melanoma risk factors and, especially if there are other clinically atypical nevi and/or a family or personal history of melanoma, additional evaluation and consideration of periodic surveillance may be appropriate. Otherwise, I believe as stated above that this lesion is consistent with a special site nevus of genital skin, which has no known particular prognostic or predictive significance.

**OVERALL COMMENT**

Despite the considerable degree of atypia in this lesion, it is within the range of changes seen in atypical genital nevi. It is, of course, judicious to be sure that these lesions have been completely excised, and fully examined histologically (MPATH DX Category 2).
CLINICAL INFORMATION
Pigmented lesion from the vulva of a 19-year-old woman.

REASON FOR CONSULTATION
I would greatly appreciate your opinion of the worrisome lesion from the vulva of a 19-year-old. The process demonstrates architectural and cytologic atypia.

FIGURE 4.2.2.1 A broad, superficial proliferation of large pigmented nevoid to epithelioid melanocytes.

FIGURE 4.2.2.2 The cells are arranged as nests and single cells along the dermal–epidermal junction. There are bridging nests.

FIGURE 4.2.2.3 The lesion is somewhat poorly circumscribed with single cells at one periphery. There are collections of mature nevus cells in the dermis, extending into the reticular dermis in a “congenital pattern.”

Dysplastic Nevus Versus Special Site Nevus
SECTION 4.2: SPECIAL SITE NEVI AND OTHER ATYPICAL PROLIFERATIONS OF GENITAL SKIN

4.2.2

**DESCRIPTION**

These sections show an excision biopsy of skin containing a quite broad, melanocytic lesion that measures about 8 mm in diameter on the slide, and is comprised of predominantly nested melanocytes arranged predominantly near the dermal–epidermal junction, with similar cells extending into the papillary dermis and upper reticular dermis. The cells in the dermis are predominantly nested and there is evidence of maturation from superficial to deep. The cells in the epidermis extend beyond the lateral borders of the dermal component in a “shoulder” pattern, and there are changes such as bridging nests and concentric fibroplasia that are architecturally consistent with melanocytic dysplasia. Cytologically, there is moderate to quite marked nuclear enlargement and irregularity and hyperchromatism of scattered lesional cell nuclei, constituting moderate to severe random cytologic atypia. There is no extensive high-level pagetoid scatter or continuous basal proliferation of uniformly atypical melanocytes, and mitotic figures are rare or absent. In summary, this is an interesting and somewhat unusual lesion, combining characteristics of a congenital pattern nevus, a dysplastic nevus, and a “special site nevus” of the vulvar skin. I do not believe this lesion is a melanoma, and I would characterize it as follows:

**FIGURE 4.2.2.4** At the other periphery, the last cells are in a nest indicating good circumscription. There is concentric fibroplasia in the dermis, and there are scattered lymphocytes and melanophages.

**FIGURE 4.2.2.5** Cytologically, the lesional cells have relatively small nuclei with dark chromatin. There is no continuous basal proliferation between the rete and no extensive high-level pagetoid scatter.
COMMENT

I cannot interpret this lesion unequivocally as a special site nevus because these lesions are typically dome-shaped papular nevi that do not have an adjacent junctional component. The adjacent junctional component in this case has attributes of severe melanocytic dysplasia and not melanoma. The dermal component is benign, with “congenital pattern features,” which does not necessarily indicate a true congenital origin. Again, I see no evidence of malignancy in the dermal component. Because of the severe dysplasia, which extends to lateral specimen margins, I would recommend an additional procedure to be sure this lesion has been completely excised, not only to rule out any significant additional pathology, but also to preclude any possibility of persistence, possible recurrence, and possible future progression of this markedly atypical lesion (MPATH DX Category 2).

OVERALL COMMENT

This lesion has many features of a dysplastic nevus and indeed may well be a dysplastic nevus rather than a “special site nevus.” In such a circumstance, it may be appropriate to evaluate this patient’s other melanoma risk characteristics, and if she should have other clinically atypical/dysplastic nevi and/or a family or personal history of melanoma, consideration of periodic surveillance of her skin may be appropriate.
4.2.3

Vulvar Nevi Versus Melanoma

Clinical Information
A 28-year-old woman with a large pigmented vulvar lesion approximately 8 to 10 cm in total size that had been present for many years. There had been a recent clinical change with evolution of a darker and somewhat linear area, which was clinically excised. Per the submitting surgeon, the more prominently pigmented area appeared completely excised with surrounding, more subtle pigmentation remaining in place. The specimen submitted as “satellite” was described as a separate distinct lesion from the main area of pigmentation.

Reason for Consultation
Please find enclosed a case that I would greatly appreciate your consultative opinion on. In addition to your diagnostic impression I would appreciate your thoughts on further management of this challenging lesion.

Description
These sections show, in the “satellite” specimen, a biopsy of skin from the vulva showing a small lesion within which there is irregular hyperpigmentation of basal keratinocytes with an increased number of small nevoid melanocytes, some arranged in nests and others as single cells, predominantly near the tips and sides of elongated rete ridges. There is slight enlargement and hyperchromatism of a few scattered lesional cells. There is no high-grade cytologic atypia, continuous basal or high-level pagetoid proliferation, and no mitotic activity. Changes, albeit subtle, appear to extend to an inked peripheral margin of the punch biopsy specimen.

Sections of the larger lesion are representative of a specimen described as “wide local excision.” Taken together, the sections show a very broad, moderately cellular lesion comprised of single and nested cells.

Figure 4.2.3.1 Scanning magnification of a small lesion submitted as “satellite” shows a region of hyperpigmentation of basal keratinocytes, with an increased number of single and a few nested melanocytes near the dermal–epidermal junction.
nevoid to small epithelioid melanocytes, arranged predominantly around the tips and sides of elongated rete ridges, and associated with hyperpigmentation of basal keratinocytes. Scattered lesional cells have slightly to moderately enlarged nuclei without prominent hyperchromatism or nuclear irregularity. There is no high-grade uniform atypia, and in general no continuous proliferation between the rete and little or no pagetoid scatter into the overlying epidermis. In the dermis, there are scattered patchy lymphocytes without extensive lichenoid inflammation or diffuse fibroplasia. The proliferation is almost entirely junctional. There may be a few lesional cells in the dermis but there is certainly no evidence of tumorigenic proliferation or mitotic activity there. The changes extend close and focally to lateral specimen margins. These appearances present considerable difficulties of interpretation, as summarized in your report, and will be interpreted descriptively as follows:

**FIGURE 4.2.3.2** Throughout much of its extent the pathology is that of a lentigo with hyperpigmentation of basal keratinocytes, slight elongation of rete ridges, and slight prominence of melanocytes.

**FIGURE 4.2.3.3** In addition, a few nests are present at the interface. There is no high-grade cytologic atypia, mitotic activity, continuous basal proliferation, high-level pagetoid proliferation, or other evidence of melanoma.
4.2.3 Sections of the larger lesion show a broad lesion characterized by elongation of rete ridges and hyperpigmentation of the basal epidermis.

FIGURES 4.2.3.4 and 4.2.3.5 There is an increased number of mainly single melanocytes along the dermal–epidermal junction. The proliferation in general does not extend into the suprapapillary plates between the rete. Lesional cell nuclei are slightly enlarged with pale chromatin.
COMMENT

As discussed above and in your report, these appearances present considerable difficulties of interpretation. The main lesion is moderately cellular; however, cytologic atypia is mild to moderate and definitive architectural features of melanoma in situ such as continuous basal proliferation or high-level pagetoid proliferation of uniformly atypical cells is lacking. Your suggestion that the changes could be consistent with a congenital nevus with atypia is plausible; however, if such were the case there would likely be a history known to the patient of presence at birth. Given that these changes are not diagnostic of melanoma, radical surgery would not seem to be appropriate at this time. However, it would be desirable, if possible, to completely remove these lesions, not only for diagnosis but in an effort to preclude the possibility of persistence, recurrence, and possible future progression (MPATH DX Category 2). If this is not possible, I would recommend careful follow-up with photographic documentation and biopsy of any areas of documented change.

OVERALL COMMENT

Melanoma is rare in the vulva of premenopausal women, but unfortunately not vanishingly so. Therefore, the possibility that these lesions represent potential precursors or risk markers for future, more significant lesions cannot be ruled out. On the other hand, there is no definitive evidence for this scenario and it is possible that these lesions will prove to be stable, benign lentiginous nevi.
4.2.4

Atypical Nevus Versus Melanoma

**Clinical Information**
A pigmented lesion of the left labia in a 13-year-old girl.

**Reason for Consultation**
I am concerned about the possibility of melanoma or significant atypia.

**Figure 4.2.4.1** A mal-embedded specimen comprised of a dermal component and a junctional component.

**Figure 4.2.4.2**

**Figure 4.2.4.3**
These sections show a moderately cellular proliferation of nevoid melanocytes, present in the dermis in the form of orderly nevus cells that show evidence of maturation from superficial to deep. There is an overlying junctional component that is moderately cellular and comprised of larger nevoid to epithelioid melanocytes. These are arranged mostly near the dermal–epidermal junction although there is slight pagetoid scatter of a few cells into the epidermis as seen in the Mart stain. In addition, the cells tend to have abundant epithelioid cytoplasm and relatively large nuclei. Although these features might raise some concern for a dysplastic or more significant process, the cellularity is relatively low without extensive continuous basal proliferation and there is no high-level pagetoid scatter. Mitotic activity is rare or absent and nuclear p16 expression is strong and bright in this atypical junctional component. I would therefore agree with your concern, although I do not believe these changes are in any way diagnostic of melanoma in this young individual and I would interpret this material to some extent descriptively as follows:
4.2.4

**DIAGNOSIS**

Skin, left labia majora: Compound nevus with intraepidermal atypical melanocytic proliferation of uncertain significance, see Description and Comment.

**COMMENT**

The atypical changes of the junctional component extend to the specimen borders. The differential diagnosis could include an atypical compound nevus of special sites of the so-called “genital nevus” pattern versus a severely dysplastic nevus. In these lesions, it is diagnostically helpful to be able to identify circumscription of the junctional component so that it is confined to the epidermis above the dermal component, which is not possible in this specimen. I would therefore recommend an additional procedure to be sure this lesion has been completely removed with a clear margin of normal tissue around the scar of this procedure and any residual lesion, and review of the reexcision specimen to rule out any more extensive or more atypical junctional component (MPATH DX Category 2). Because of the differential diagnosis of a severely dysplastic nevus, it may be appropriate to evaluate this patient’s other risk factors for melanoma, and especially if she should have other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance may be appropriate.

**OVERALL COMMENT**

Although positive p16 staining often is present in a melanoma, the mere presence of staining at a minimum indicates that chromosome 9p21 loss cannot have occurred, which is the only chromosomal finding that has evidence-based support as a predictor of aggressive behavior (11). In addition, the pattern of staining with strong nuclear staining as well as cytoplasmic staining is reasonably characteristic of benign nevi in general. Comparative genomic hybridization or fluorescence in situ hybridization can be considered for lesions of this type; however, I believe that the presence of p16 staining makes this genomic testing less likely to be informative.
4.2.5

Spindle Cell Nevus Versus Melanoma

**CLINICAL INFORMATION**
Lesion of the dorsal penile shaft in a 17-year-old.
Patient reports 12 days duration!

**REASON FOR CONSULTATION**
Spindle cell Spitz, but?

**FIGURE 4.2.5.1** A plaquelike lesion, comprised of spindle cells that are quite uniform from side to side.

**FIGURE 4.2.5.2** The lesion is well circumscribed at its periphery. The lesional cells contain moderately abundant melanin pigment in relatively coarsely divided granules.

**FIGURE 4.2.5.3** The lesional cells are quite uniform and tend to be vertically oriented. There is a tendency to confluence of nests in this particular example. Mitotic figures can be quite numerous in these lesions in their junctional components, and one is seen near the epidermis at the bottom left of this image.
DESCRIPTION

These sections show a shave biopsy of skin from the dorsal shaft of the penis, containing a moderately to highly cellular proliferation of narrow elongated spindle cells, relatively uniform from side to side and forming a relatively symmetrical lesion about 3 mm in diameter but extending to one specimen margin, and less than 1 mm in depth. There is moderate pigment especially at the periphery of the lesion. In the center, it is more cellular, with lesional cells protruding into the papillary dermis but without tumorigenic proliferation. Junctional mitoses are fairly numerous and there are also some mitoses apparently in the dermal component, although it is not clear whether some of these are in clusters of cells that are connected to the epidermis despite being near the base of this relatively superficial lesion. Taking these findings together and also taking into consideration the patient’s youthful age group, I believe these findings are quite compatible with a pigmented spindle cell nevus of Reed, albeit with only slight pigmentation, especially toward the center of the lesion and near the base. There are some atypical features, including the lack of pigment, and also a somewhat more cellular dermal component, and more numerous junctional/dermal mitoses, than one usually sees. In summary, I would interpret this lesion as follows:

FIGURES 4.2.5.4 and 4.2.5.5 Only a few lesional cells are present in the papillary dermis at the base of the lesion and they show evidence of maturation to a smaller nevoid and nonspindled cell type.
COMMENT

Although I believe this is a benign lesion, it is usual to recommend complete excision of these cellular proliferative lesions, if only because occasionally some of them have shown evidence of recurrence with increased atypia, causing difficulties of interpretation. I would therefore recommend an additional procedure to be sure this lesion has been removed with a narrow but clear margin of normal tissue (MPATH DX Category 2).

OVERALL COMMENT

This is an unusual location for this lesion, but the appearances are quite characteristic and differ from those expected to be seen in atypical nevi of the genital type, and also from dysplastic nevi and melanoma. Numerous mitoses in this lesion are consistent with its history of recent onset, and junctional mitoses are commonly seen in pigmented spindle cell nevi. Dermal mitoses would represent a more concerning finding. Maturation of the dermal component is a key feature in the diagnosis of pigmented spindle cell nevus. Pigmented spindle cell nevi are unusual in this site; however, they are relatively common simulants of melanoma and are discussed again in Section 7.2.
4.2.6

Vulvar Nevus Versus Dysplastic Nevus Versus Melanoma

**CLINICAL INFORMATION**
Pigmented lesion on the vulva of a 13-year-old. Rule out atypia.

**REASON FOR CONSULTATION**
Is this a dysplastic nevus or a melanoma?

**FIGURE 4.2.6.1** A broad, superficial moderately to highly cellular melanocytic proliferation.

**FIGURE 4.2.6.2 and 4.2.6.3** The lesion is reasonably well circumscribed at its right and left peripheral borders.
CASE 6: VULVAR NEVUS VERSUS DYSPLASTIC NEVUS VERSUS MELANOMA

DESCRIPTION

These sections show a broad, moderately to rather highly cellular proliferation of spindle to epithelioid and nevoid melanocytes in the epidermis and superficial dermis. In the junctional component, the cells are arranged mainly in nests, mainly near the dermal–epidermal junction, although there are also single cells and some of these extend into the epidermis in a pagetoid scatter pattern, although generally not beyond the lower middle third. There are some nests that bridge between adjacent rete ridges in the pattern of a dysplastic nevus. A few clusters of cells enter the dermis, without clear evidence of tumorigenic proliferation and without mitotic activity. The epidermis is intact without ulceration and there is no evidence of “consumption of the epidermis.” This lesion is not a Spitz nevus/tumor because it is not comprised of large spindle and/or epithelioid melanocytes and there are no Kamino bodies. Importantly, occasional keratinocyte mitoses are seen, but lesional cell mitoses are rare or absent in both junctional and dermal components. Taking these findings together, especially in the context of a young teenager and in the special site of the vulva, I would consider that this lesion in all likelihood represents an atypical “special site nevus” of the genital type. Atypical features in this case include its predominantly junctional nature since the original descriptions of atypical genital nevi described papular compound lesions rather than broad, predominantly junctional lesions. Nevertheless, I have seen examples of genital nevi with this general architecture. The differential diagnosis could also include a severely dysplastic nevus. Again, in the context of a young individual I do not believe these changes are

FIGURE 4.2.6.4 The lesion is comprised of nevoid to spindle-shaped melanocytes arranged in nests that tend to become confluent along the dermal–epidermal junction. In the dermis there is a patchy lymphocytic infiltrate with melanophages and fibroplasia.

FIGURE 4.2.6.5 Lesional cells enter the papillary dermis while showing little evidence of maturation. Mitotic figures are not identified.
diagnostic of melanoma arising in a dysplastic nevus. Given these somewhat conflicting findings and the differential diagnosis described, I would interpret this lesion descriptively as follows:

**DIAGNOSIS**

Skin, vulva: Superficial atypical melanocytic proliferation of uncertain significance, most consistent with an atypical special site nevus of genital skin, extending to a peripheral specimen margin, see Description and Comment.

**COMMENT**

As noted, I favor a special site nevus or a severely dysplastic nevus. Because of the latter differential diagnosis, I would recommend evaluation of this patient’s other melanoma risk factors, and especially if she should have other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance as she goes through life would be appropriate. Of course, if this is an atypical genital nevus, these are usually isolated findings of no particular significance. Nevertheless, because of the close or positive margin, I would recommend an additional procedure to be sure this lesion has been completely removed with, at a minimum, a margin of normal tissue around the scar of this procedure and any residual lesion (MPATH DX Category 2). Follow-up of the lesional site would also be appropriate, at least for a few years.

**OVERALL COMMENT**

As noted above in the original descriptions, atypical genital nevi were papular lesions with atypia of the junctional component and superficial dermal cells, which showed evidence of maturation to a smaller cell type at the base. More recently, predominantly junctional lesions or lesions with an adjacent junctional component have been identified that seem to fit into this general category.
5.0 Superficial Atypical Melanocytic Proliferations of Special Sites

5.0.1 Severe Melanocytic Dysplasia Versus Evolving Melanoma In Situ Versus Special Site Nevus of the Skin of the Breast
5.0.2 Special Site Nevus Versus Dysplastic Nevus
5.0.3 Special Site Nevus Versus Dysplastic Nevus Versus Melanoma
5.0.4 Special Site Nevus Versus Traumatized Nevus Versus Dysplastic Nevus Versus Melanoma
5.0.5 Special Site Nevus Versus Dysplastic Nevus Versus Melanoma
5.0.6 Special Site Nevus Versus Dysplastic Nevus
5.0.7 Special Site Nevus Versus Severely Dysplastic Nevus
5.0.8 Special Site Nevus Versus Dysplastic Nevus
5.0.9 Special Site Nevus Versus Severely Dysplastic Nevus or Melanoma of the Ear
In addition to lesions of acral skin and of genital skin, which may also be regarded as special sites, there is a substantial literature that has identified variations in nevus architecture and cytology related to a variety of different locations in the skin, termed “special site nevi” or “nevus of special sites (NOSS).” This designation has been applied to nevi of flexural skin (axilla, umbilicus, inguinal creases, pubis, scrotum, and perianal area), and to the skin of the breast, the ear, the scalp, and the distal lower extremity (1–9). Some of these lesions have been related to the embryonic milk line (breast, axilla, umbilicus, genitalia) (10).

Key features of NOSS have been well described by Mason, Mohr, Koch, and Hood (10). These include a tendency to occur in the embryonic milk line/flexural sites listed above. However, the atypical NOSS are not unique to any site, and not all nevi that occur in the special sites fall into this special category. Rather, the majority of nevi in these sites are unremarkable nevi of the usual pattern. The nomenclature of NOSS is not standardized, and other names include atypical genital nevi, atypical melanocytic nevus of the genital type, melanocytic acral nevus with intraepithelial accent of cells, acral-lentiginous nevus of plantar skin, atypical nevi of the scalp, and special site nevi.

Because of the locations in which they occur, most NOSS do not have severe chronic solar damage (CSD), and therefore are “low CSD” or “no CSD” lesions. No doubt there are exceptions; however, in our opinion a diagnosis of a NOSS in a high CSD location such as the ear or the bald scalp of an older male, or the upper part of the breast in a woman or man who has severe solar damage in that location, should be made with great circumspection, and the possibility that the lesion is a melanoma should be seriously considered. In particular the ear is a not uncommon location for melanoma in older men, although not in women, providing some evidence for the solar hypothesis of melanoma development (11,12).

The important feature of NOSS is that they may have histologic features in common with melanoma (and also dysplastic nevi), yet they are considered to be benign lesions and have not been demonstrated to have significance as markers of increased risk for melanoma beyond that which is associated with common acquired nevi and small congenital nevi. The nevi of flexural/midline skin, genitalia, and scalp tend to share similar histology, namely notably enlarged junctional nests with diminished cohesion of melanocytes—a “large nested and dyshesive pattern.” As a generalization, ear and breast NOSS are more atypical than nevi at other sites, and scalp and acral NOSS have prominent pagetoid spread. The definitive diagnosis of a nevus of special sites is often ambiguous because special sites are not exempt from a diagnosis of an authentic dysplastic nevus or melanoma and these lesions share common histologic features. Nevertheless, it is generally agreed that NOSS possess some distinctive microscopic features (10).

The different NOSS have somewhat variable features as well as features in common with each other and with dysplastic nevi and melanomas. Flexural NOSS are said to display greater variability in the size of junctional nests as well as the location of nests at the edges of rete ridges and between the rete, and to have junctional “shoulders,” overlapping in these features with dysplastic nevi. They lack cytologic atypia and stromal reactions typical of dysplastic nevi. Breast and scalp nevi are more likely to express pagetoid scatter, similar to acral nevi. Cytologic atypia is said to be more prominent in nevi from the ear. Features of NOSS that indicate their benign nature include a general lack of cytologic atypia (although this may be present and quite severe in some instances), generally lower cellularity, lack of or lesser degrees of pagetoid scatter or continuous basal proliferation, and lack of mitotic activity especially in the dermal component as well as the presence of maturation of the
dermal component. Clinically, these lesions usually present as stable lesions often without marked clinical atypia and are often diagnosed clinically as compound nevi of no special type.

NOSS are thought to have a similar prognosis to other nevi, and are not known to have the same significance as markers of risk for future development of melanoma as do dysplastic nevi and melanomas. However, their long-term behavior is unknown and surgical excision with clear margins is recommended for all of these lesions. Consideration of clinical follow-up may also be appropriate in some cases (10).

In my experience, definitive criteria to make a distinction among the possibilities of a nevus of special sites, a dysplastic nevus, or superficial melanoma are often lacking. In these circumstances, it seems best to provide a descriptive diagnosis such as “intraepidermal atypical melanocytic proliferation of uncertain significance (IAMPUS)” or “superficial atypical melanocytic proliferation of uncertain significance (SAMPUS),” the latter term being used when there may be a few atypical cells in the dermis (13). The differential diagnosis should be expressed including, when applicable, microstaging attributes that might be appropriate if the lesion were interpreted as a melanoma.

When the differential diagnosis includes a dysplastic nevus, it is appropriate to evaluate the patient for other risk factors for melanoma, and especially if there are other clinically atypical or dysplastic nevi and/or a family or personal history of melanoma, consideration of periodic surveillance is especially appropriate. It is possible that a dysplastic nevus, on any body site including a special site, can serve as a marker of an individual who is at increased risk for melanoma and who might also be a member of a family at increased risk for melanoma. In such a circumstance, the individual or the family can be offered surveillance with the aim of recognizing any future development of melanomas at a curable early stage.

NOSS should in general be completely excised (10) (MPATH DX Category 2 or 3 if there is uncertainty regarding the possibility of melanoma) to allow for complete histologic examination and also hopefully to preclude any possibility of persistence, recurrence, or future progression even though this, at least theoretically, is not likely to occur with these lesions.

References

5.0.1

Severe Melanocytic Dysplasia Versus Evolving Melanoma In Situ Versus Special Site Nevus of the Skin of the Breast

CLINICAL INFORMATION
Lesion of breast from a 45-year-old woman.

REASON FOR CONSULTATION
I would like to rule out the possibility of melanoma in this lesion.

DESCRIPTION
Sections show a small and reasonably well circumscribed lesion that is comprised of uniformly atypical small to large epithelioid melanocytes, and measures less than 3 mm in diameter on the slide. The lesional cells are arranged singly and in nests along the dermal–epidermal junction. Rete ridges are somewhat elongated, but there are no well-developed bridging nests. Cytologically, the lesional cells have abundant cytoplasm with finely divided melanin pigment, and many of them have quite large irregular and hyperchromatic nuclei. Only a few cells rise slightly above the junction. Mitotic figures are rare or absent. In the dermis, there is a patchy to focally bandlike lymphocytic infiltrate with diffuse fibroplasia and melanophages. There is no invasion and certainly no tumorigenic proliferation or mitotic activity in the dermis. Taking these findings together, this lesion is difficult to interpret. The differential diagnosis could include evolving or early established melanoma in situ, or severe melanocytic dysplasia of the epithelioid cell type. The latter would be favored by the architecture but the cytologic atypia is somewhat more severe than one expects to see. The differential

FIGURE 5.0.1.1 A small superficial lesion with a dense lymphocytic infiltrate and an asymmetrical profile. There is a somewhat “large nested and dyshesive” pattern of the junctional profile.
CASE 1: SEVERE MELANOCYTIC DYSPLASIA VERSUS EVOLVING MELANOMA

5.0.1

FIGURE 5.0.1.2 There is a moderately cellular proliferation of nevoid to epithelioid melanocytes in the epidermis.

diagnosis could also, no doubt, include a so-called special site nevus of breast skin. Because of these conflicting criteria, I will interpret this lesion descriptively as follows:

FIGURES 5.0.1.3 and 5.0.1.4 There is moderate atypia of lesional cells in the form of nuclear enlargement, irregularity, and hyperchromatism in a few scattered lesional cells (moderate to severe random cytologic atypia). Mitotic figures are not observed.
As discussed above, this lesion presents considerable difficulties of interpretation. Because of the differential diagnosis of severe melanocytic dysplasia or evolving melanoma in situ, it would be appropriate to consider this patient’s other risk factors for melanoma, and especially if there are other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance may be appropriate. If this lesion is a so-called special site nevus of the breast, it should have no significant adverse implications. Nevertheless, complete excision is appropriate to preclude any possibility of persistence, recurrence or progression of this atypical lesion.

There is no gold standard to precisely determine the significance of this lesion; however, in my opinion the changes fall short of criteria for melanoma, while not conforming well to descriptions of special site nevi of the breast. Although lacking some architectural features, the appearances could be consistent with severe melanocytic dysplasia, in which case the pagetoid scatter and atypia would be concerning for evolving melanoma in situ. Complete excision is appropriate management for this atypical lesion (MPATH DX Category 2). This present lesion is completely excised and would require no further treatment.
5.0.2

Special Site Nevus Versus Dysplastic Nevus

**CLINICAL INFORMATION**
Pigmented lesion of the left nipple in a 47-year-old woman.

**REASON FOR CONSULTATION**
I cannot rule out melanoma in this lesion.

**DESCRIPTION**
These sections show a small biopsy stated to be from the left nipple of a 47-year-old woman, containing a moderately cellular proliferation of large nevoid to epithelioid melanocytes, arranged predominantly in nests, predominantly near the dermal–epidermal junction. There is a tendency to confluence of nests and there is a focal tendency to clefting and dyshesion artifact. In the dermis, there are patchy lymphocytes. There is no evidence of any invasive, tumorigenic, or mitogenic proliferation in the dermis. Cytologically, the lesional cells have abundant cytoplasm with relatively finely divided melanin pigment. The nuclei are relatively small, without marked irregularity or hyperchromatism. There are a few scattered larger somewhat hyperchromatic nuclei. Mitotic figures are rare or absent. Taken together, this lesion demonstrates a combination of architectural and cytologic atypia, concerning for severe dysplasia and/or evolving melanoma in situ. The differential diagnosis would also include a so-called special site nevus of the breast. I do not believe it is possible to reliably distinguish among these possibilities, and I would therefore interpret this lesion descriptively as follows:

![Image](image.png)

FIGURE 5.0.2.1 A junctional proliferation of large nevoid to epithelioid melanocytes.
FIGURE 5.0.2.2 The epidermis is irregularly thickened and thinned, and there is fibroplasia in the dermis.

FIGURE 5.0.2.3

FIGURE 5.0.2.4

FIGURE 5.0.2.5

FIGURES 5.0.2.3–5.0.2.5 There is pagetoid of scatter of nests and single cells into the epidermis focally into the upper third, and there is moderate to severe uniform atypia of lesional cell nuclei. In addition, the cells have abundant cytoplasm containing finely divided “dusty” melanin pigment granules.
COMMENT

As noted above, the differential diagnosis includes a severely dysplastic nevus, which could be associated with increased risk for melanoma. Especially if this patient should have other clinically atypical nevi or a family or personal history of melanoma, periodic surveillance of her skin may be indicated. There are also changes concerning for evolving or early established melanoma in situ with positive margins, and I would recommend an additional procedure to be sure this lesion has been completely removed. If this lesion is a special site nevus of the breast, then it would have no particular significance. However, as noted above, I believe it should be completely removed with a margin of normal tissue around the scar of this procedure and any residual lesion.

OVERALL COMMENT

This lesion presents cytologic and architectural features that are very concerning for melanoma in situ; however, it is apparently a small lesion, there are no mitoses, and the location on the nipple is obviously unusual for melanoma. Pigmented Paget’s disease could be considered in a case like this and could be ruled out with a keratin stain and/or CEA. Melan-A staining alone could be misleading because it could react with pigment granules in nonmelanocytic cells. Complete excision is appropriate management (MPATH DX Category 2).
CLINICAL INFORMATION
F22, atypical pigmented lesion of the areola.

REASON FOR CONSULTATION
While breast nevi are commonly associated with atypia, the confluence, upward spread, and cytologic atypia are prominent. These changes are worrisome for melanoma in situ arising in a nevus.

DESCRIPTION
Sections show a punch biopsy of skin from the areola, containing smooth muscle bundles consistent with the site. Within the epidermis and superficial dermis, there is a moderately to focally rather highly cellular proliferation of nevoid to epithelioid melanocytes, arranged in the epidermis in ill-defined nests and as single cells, with quite extensive pagetoid scatter of lesional cells across much of the extent of the lesion, in many cases rising to the level of the stratum granulosum. Cytologically, the cells have relatively abundant cytoplasm, with moderate finely to coarsely divided melanin pigment granules. Some of the cells have enlarged, irregular, and hyperchromatic nuclei, and some of them have nucleoli. I would agree that these changes are very concerning for melanoma in situ. On a more reassuring note, mitotic figures appear to be rare or absent. Immunostains (not shown) were available for review. Ki-67, although somewhat difficult to interpret due to artifact associated with antigen retrieval, is negative in the few dermal cells that can be visualized. HMB 45 stains the junctional component quite brightly and also a few dermal cells of uncertain significance. It is therefore not convincingly “top heavy.” Reactivity for p16 is present although predominantly cytoplasmic, at least in some

FIGURE 5.0.3.1 There is a broad, relatively sparsely cellular proliferation of nevoid to epithelioid melanocytes in the epidermis.
of the cells. Given these conflicting findings, I find this difficult to interpret; however, the possibility of melanoma cannot be ruled out despite this uncommon location (although not vanishingly so) for melanoma. I would therefore interpret this lesion descriptively as follows:

**FIGURES 5.0.3.2–5.0.3.4** Single cells tend to predominate over nests in many areas, and there is pagetoid scatter into the upper third of the epidermis. There is no actinic elastosis in the dermis.
5.0.3

**COMMENT**

This lesion presents many features of a superficial spreading melanoma; however, I am held back from making a more definitive interpretation by the lack of proliferative activity, the youthful age of the patient, and the unusual location. It would be of interest to know if there has been any history of UV exposure at the site (e.g., sunbed use). The differential diagnosis could also include an atypical “special site nevus” of the breast; however, this lesion does not show the more typical “large nested and dysplastic” pattern described in these lesions. The lesion also perhaps has some Spitzoid attributes, although neither the cytology nor the architecture are characteristic. One might also consider a severely dysplastic nevus. In the worst-case scenario, this lesion would be a superficial spreading melanoma, at least in situ, though with a few atypical single cells of uncertain significance in the dermis. The lesion appears to be completely excised, with closest borders of less than 1 mm to atypical cells of the junctional component. On balance, I would favor considering this lesion as a severely dysplastic nevus. However, I would recommend management of this lesion with the above differential diagnosis taken into consideration (MPATH DX Category 2 or 3, depending on clinicopathologic correlation and patient and physician preference).

**OVERALL COMMENT**

This lesion presents a good example of disparate diagnostic considerations including (in order of biologic significance) a special site nevus of the breast, a pagetoid Spitz nevus/proliferation, a severely dysplastic nevus, or a nontumorigenic nonulcerated nonmitogenic predominantly in situ melanoma. The prognosis for cure of this particular lesion is excellent no matter what the given diagnosis. Fluorescence in situ hybridization (FISH) could potentially provide additional diagnostic information. Management of a lesion of this sort by complete excision is appropriate.
5.0.4

Special Site Nevus Versus Traumatized Nevus Versus Dysplastic Nevus Versus Melanoma

**CLINICAL INFORMATION**
A 3 mm papule from the left areola of a 24-year-old woman.

**REASON FOR CONSULTATION**
I would appreciate a second opinion on the enclosed lesion. Microscopically, I see a markedly atypical melanocytic lesion in early compound configuration. Of course, nevi on and around the breast may display a greater number of atypical features than nevi from other sites. However, atypia in this lesion far exceeds that which has been reported. Indeed, the small expansile nodule of highly atypical melanocytes seen in the superficial dermis of recut level one is very disconcerting, although I do not see convincing mitoses. Because of the cosmetically critical site, I would be very grateful for your assessment.

**DESCRIPTION**
These sections show a shave biopsy of skin, containing a moderately cellular melanocytic lesion, comprised in its junctional component of single and

![Image of the lesion](image_url)

**FIGURE 5.0.4.1** A broad lesion with an irregular distribution of cells in the epidermis and with the lymphocytic infiltrate and fibroplasia in the dermis.
section 5.0:
superficial atypical melanocytic proliferations of special sites

5.0.4

nested melanocytes arranged along the dermal–epidermal junction. Focally, there are nests bridging between adjacent rete ridges, in a pattern consistent with melanocytic dysplasia. Cytologically, the lesional cells are quite large, with relatively abundant amphophilic cytoplasm and moderately enlarged nuclei with moderate to severe pleomorphism and hyperchromatism. I agree that these changes, which are asymmetrically distributed within the lesion, exceed those which one might attribute to a “special site.” There is also diffuse fibroplasia and a bandlike lymphocytic infiltrate in the papillary dermis. These changes are reminiscent of the fibrosing dysplastic nevi that have been described by several groups. In any event, I do not believe these changes reach criteria for melanoma; however, I would characterize this lesion as severely dysplastic as follows:

**FIGURES 5.0.4.2–5.0.4.5** The cells in the epidermis are relatively large with abundant cytoplasm and finely divided melanin pigment. Their nuclei are generally small. There is extensive dermal fibroplasia.
**CASE 4: SPECIAL SITE NEVUS VERSUS TRAUMATIZED NEVUS**

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**DIAGNOSIS**

Skin, left areola: Superficial atypical melanocytic proliferation of uncertain significance (SAMPUS), most consistent with a compound nevus with severe dermal and epidermal melanocytic dysplasia, extending to specimen margins, see Description and Comment.

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**COMMENT**

I could not rule out the possibility in a lesion with this degree of atypia of potential for local persistence, recurrence, and progression. I would therefore recommend consideration of an additional procedure to be sure it has been completely removed, or perhaps careful follow-up of the lesional site.

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**OVERALL COMMENT**

The extended differential diagnosis for this superficial atypical melanocytic proliferation could include a special site nevus of the breast, a traumatized fibrosing nevus, a severely dysplastic nevus, or even an evolving melanoma at least in situ. Complete excision for a lesion of this type is appropriate, or perhaps careful follow-up, especially if the patient has other clinically atypical nevi as an indication for follow-up and if the lesion has been clinically excised (MPATH DX Category 1 or 2).


**5.0.5**

*Special Site Nevus Versus Dysplastic Nevus Versus Melanoma*

**CLINICAL INFORMATION**
Lesion of the upper right breast in a 42-year-old woman.

**REASON FOR CONSULTATION**
Clin: “R/O ATN”
Our Ddx: severely atypical CN versus MM

**DESCRIPTION**
These sections show a shave biopsy of skin containing a moderately to highly cellular lesion, which presents considerable difficulties of interpretation. At the periphery of the lesion, there are predominantly nested melanocytes arranged predominantly near the dermal–epidermal junction, with some bridging nests, in a pattern of melanocytic dysplasia. The cells tend, however, to be relatively large with abundant epithelioid cytoplasm and large, somewhat irregular and hyperchromatic nuclei. Toward the center of the lesion, similar cells protrude into the papillary dermis and into the upper reticular dermis, showing only very limited evidence of maturation from superficial to deep. Again they have abundant amphophilic cytoplasm with finely divided melanin pigment. These are very concerning features; however, the cells are arranged in small nests separated by collagen fibers, without tumorigenic proliferation, and there is no mitotic activity evident in multiple section planes available for review. In the absence of proliferative activity, ulceration, or tumorigenic proliferation, I

**FIGURE 5.0.5.1** Scanning magnification shows a fairly small lesion with the dermal component asymmetrically placed within the junctional component. There is little or no actinic elastosis.
believe these changes could be compatible with a nevus with severe dermal and epidermal dysplasia. However, at least one junctional lesional cell mitosis is present, which I believe indicates that the lesion as a whole has proliferative potential. The differential diagnosis could include a Spitz tumor; however, the cytology is not that of large spindle and/or epithelioid cells. The differential diagnosis could also include a so-called special site nevus of the breast; however, the large nested and dyshesive pattern described in these lesions is not observed, and these lesions are not typically characterized by such severe atypia. Given the presence of severe uniform atypia coupled with failure of maturation of the dermal component, and despite the lack of dermal mitoses, the finding of a junctional lesional cell mitosis leads me to conclude that this lesion is best interpreted as a melanoma, which I would characterize as follows:

FIGURE 5.0.5.2 The lesion is poorly circumscribed at its periphery.

FIGURE 5.0.5.3

FIGURE 5.0.5.4

FIGURES 5.0.5.3–5.0.5.5 Lesional cells in the superficial dermis resemble those of the base indicating that there is little evidence of maturation.
section 5.0: superficial atypical melanocytic proliferations of special sites

5.0.5

FIGURE 5.0.5.6 There is severe atypia; however, this is not uniform with some cells having quite small nuclei and with a suggestion of maturation in this portion of the lesion.

DIAGNOSIS

Skin, upper right breast: Malignant melanoma, superficial spreading type, with nontumorigenic and nonmitogenic accretive vertical growth phase, Clark’s level IV, greatest Breslow thickness 0.64 mm, see Description and Comment.

COMMENT

Accretive vertical growth phase is a form of dermal tumor that is comprised of clusters of cells that are not larger individually than those in the epidermis yet are piled on top of one another in an accretive pattern to form a nodule. The prognosis for this AJCC stage Ia lesion should be excellent. The dermal mitotic rate is zero, tumor-infiltrating lymphocytes are essentially absent, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. Changes extend within a fraction of a millimeter of the specimen base and margins and I would, of course, recommend definitive therapy for this lesion based on the above diagnosis (MPATH DX Category 4).
The upper breast is a potentially sun-exposed area; however, in this biopsy there is little or no solar elastosis, which is unusual for melanoma and raises the possibility of an unusual nevoid lesion. Nevertheless, based on the severe cytologic atypia and architectural features, I would consider this to be a lesion that could have capacity for local persistence, recurrence, and future progression if not completely excised but would be likely to have little or no competence for metastasis.
5.0.6

Special Site Nevus Versus Dysplastic Nevus

**CLINICAL INFORMATION**

F11, Lesion of scalp.

**REASON FOR CONSULTATION**

Is there significant atypia in this lesion of an 11-year-old girl?

**DESCRIPTION**

These sections show a punch biopsy of skin with large scalp hairs. There is a somewhat subtle proliferation of moderately enlarged epithelioid and nevoid melanocytes along the dermal–epidermal junction. There are a few similar cells in the dermis showing evidence of maturation along nevic lines. Although the differential diagnosis for this lesion could include epithelioid melanocytic dysplasia, the patient is young and the lesion is located on the scalp, which is also a so-called special site in which atypical changes may be ascribed to the lesional location. I would therefore interpret this lesion descriptively as follows:

**FIGURE 5.0.6.1** Punch biopsy specimen of skin of the scalp.

**FIGURE 5.0.6.2** There is a junctional proliferation of melanocytes, predominantly arranged in nests.
The cells have moderately abundant cytoplasm with finely divided melanin pigment. There is moderate nuclear enlargement and slight irregularity and hyperchromatism.
COMMENT

Although I believe the changes are most likely consistent with a special site nevus of the scalp, the possibility of a dysplastic nevus with mild to moderate atypia could also be considered; however, the lesion is small, and cytologic atypia is not prominent. Given the differential diagnosis of melanocytic dysplasia, it might be appropriate to assess this patient's other risk factors for melanoma and if she should have other clinically atypical nevi and/or a family history of melanoma, additional evaluation and possible surveillance might be indicated. I do not believe there is evidence of melanoma in these lesions.

OVERALL COMMENT

It is not uncommon to clinically find dysplastic nevi in the scalp of children who are members of hereditary melanoma kindreds. Melanomas of the scalp also occur, but are very rare, especially, of course, in this pediatric age group. Although in general special site nevi should be completely excised if only for complete evaluation, surveillance might be appropriate in this age group (MPATH DX Category 1 or 2).
5.0.7

Special Site Nevus Versus Severely Dysplastic Nevus

CLINICAL INFORMATION
Pigmented lesion of the scalp in a 20-year-old woman. Rule out atypia.

REASON FOR CONSULTATION
This lesion demonstrates severe epidermal and dermal atypia, which appear more prominent than usually seen in a “special site” nevus. This could be a “special site” nevus with overlapping features of a severely atypical dysplastic nevus. I am also concerned about the presence of dermal atypia. Therefore I would like to get a second opinion.

DESCRIPTION
These sections show a relatively broad, moderately cellular proliferation of relatively large epithelioid

FIGURE 5.0.7.1 A broad, superficial more or less symmetrical lesion.

FIGURE 5.0.7.2

FIGURE 5.0.7.3

FIGURES 5.0.7.2 and 5.0.7.3 At the right edge, the last cells are arranged in a nest.
to nevoid melanocytes, arranged predominantly in nests, predominantly near the tips and sides of elongated rete ridges, with nests bridging between adjacent rete. Cytologically, the cells have abundant epithelioid cytoplasm with finely divided melanin pigment, and they exhibit moderate to focally severe nuclear atypia in the form of enlargement, membrane irregularity, and hyperchromatism. A rare lesional cell mitosis is also identified in the junctional component. This is a concerning finding for the possibility of melanoma; however, in the absence of more extensive high-level pagetoid or continuous basal proliferation, I believe this lesion is best interpreted as a severely dysplastic nevus. There are clusters of cells in the dermis similar to those in the epidermis showing only slight evidence of maturation; however, there is no dermal mitotic activity or tumorigenic proliferation. I do not believe this lesion is a so-called special site nevus of the scalp. I believe there is considerable overlap, but the features of this lesion are much more characteristic of a dysplastic nevus. I note also that this lesion was submitted with the clinical impression “rule out dysplastic nevus.” I would therefore interpret this lesion as follows:
COMMENT

The significance of a single dysplastic nevus may be relatively small; however, severely dysplastic nevi have been associated with an approximately fourfold relative risk for melanoma in two studies. If this lesion were a special site nevus of the scalp, there has been no such association demonstrated. If this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, her risk would be greater and certainly consideration of surveillance would be warranted. This present lesion extends close or to lateral specimen margins and because of the diagnosis of severe dysplasia as well as its possibly difficult to follow location, I would recommend consideration of an additional procedure to be sure it has been completely excised, or perhaps careful follow-up of the lesional site if this can be accomplished (MPATH DX Category 1 or preferably 2).

OVERALL COMMENT

Clinical and histologic appearances in this case favored a dysplastic nevus; however, the possibility that it is actually a “special site nevus” of the scalp should perhaps be entertained. In any event, the significance of a single dysplastic nevus is relatively small although increased by the presence of severe histologic dysplasia.
5.0.8

Special Site Nevus Versus Dysplastic Nevus

CLINICAL INFORMATION
Pigmented lesion of the wrist in a 10-year-old child; rule out atypia.

REASON FOR CONSULTATION
Is there significant atypia in this lesion from the wrist of a young child?

DESCRIPTION
These sections show a punch biopsy of skin from a 10-year-old child, containing a moderately to focally more highly cellular intraepidermal proliferation of nevoid to epithelioid melanocytes, arranged predominantly in nests and also as single cells, predominantly along the dermal–epidermal junction. A few cells are slightly above the junction; however, there is no extensive high-level pagetoid proliferation, and in addition there is no extensive continuous basal lentiginous proliferation. Cytologically, there is generally moderate to focally more severe nuclear size, shape, and staining variation. There are no lesional cell mitoses. In the dermis, there are patchy perivascular lymphocytes and melanophages. These appearances present considerable difficulties of interpretation. I would agree that there could be concern for melanoma in situ or evolving melanoma in situ versus severe melanocytic dysplasia. However, I note that this lesion is from the wrist, which could be considered a so-called special site, and perhaps this phenomenon of a flexural special site could account for some of the atypical features. The lesion does not fit with cytologic criteria for a Spitz or pigmented spindle cell nevus; however, these possibilities cannot entirely be excluded. In any event, especially in a 10-year-old child, I do not believe these changes are diagnostic of melanoma in situ or any other specific entity and would therefore characterize it as follows:

FIGURE 5.0.8.1 A punch biopsy of skin, containing a small, well-circumscribed but not especially symmetrical lesion. The lesion is comprised of predominantly nested melanocytes in the epidermis.

FIGURE 5.0.8.2 It is well circumscribed at the periphery with the last cells in a nest.
FIGURE 5.0.8.3 AND 5.0.8.4 There are also single cells that rise slightly above the junction focally. There is some evidence of dyshesion artifact in some of the nests.

FIGURE 5.0.8.5 The nuclei are small and regular without marked hyperchromatism. There is a patchy lymphocytic infiltrate with melanophages in the dermis.
COMMENT
As noted above, I cannot rule out a severely dysplastic nevus or evolving melanoma in situ; however, alternative possibilities exist as discussed above. Because of the differential diagnosis, and because changes extend to a lateral specimen margins, I would recommend an additional procedure to be sure this lesion has been completely removed with, at a minimum, a margin of normal skin around the scar of this procedure and any residual lesion (MPATH DX Category 2). Because of the differential diagnosis of severe dysplasia I would also recommend assessment of this patient’s other melanoma risk factors, and if he should have other clinically atypical nevi and/or a family history of melanoma, additional evaluation and possible surveillance may be indicated.

OVERALL COMMENT
If this lesion were a dysplastic nevus it would be histologically “mild,” except for the presence of focal pagetoid scatter. In any event, cytologic atypia is minimal and the significance of this lesion is likely slight if any.
5.0.9

Special Site Nevus Versus Severely Dysplastic Nevus or Melanoma of the Ear

CLINICAL INFORMATION
Atypical pigmented lesion of the ear in a 41-year-old woman.

REASON FOR CONSULTATION
In my opinion this is a borderline melanocytic lesion for which the differential includes a dysplastic nevus with spindle cell features and severe atypia and malignant melanoma. Concerning features with regard to the latter possibility include the breadth of the atypical junctional component with discontinuous areas of confluent growth, prominent disorganization, and a fairly prominent pagetoid extension. In addition, evaluation of the dermal component is constrained to two prominent adnexal extensions such as that, if regarded as melanoma, it is difficult to dismiss the possibility that superficial dermal invasion has occurred. In view of the borderline nature of this lesion with conflicting histologic criteria, age of the patient, and occurrence of this lesion in a cosmetically sensitive location, consultative opinion will be obtained.

DESCRIPTION
These sections show a shave biopsy of skin, containing a highly cellular proliferation of large epithelioid melanocytes, arranged singly and in nests, predominantly along the dermal–epidermal junction, but with areas of pagetoid extension into the epidermis, focally to the stratum corneum. Although the differential diagnosis could certainly include a severely dysplastic nevus, the pagetoid scatter is quite well-developed in focal areas, and there is marked confluence of nests with some areas of continuous confluent proliferation along the junction. As you also note, there is extension of lesional cells down around skin appendages. I do not believe this lesion is a Spitz nevus/tumor, because the cells are not uniformly large spindle and/or epithelioid cells from side to side across the lesion.

FIGURE 5.0.9.1 An asymmetrical, highly cellular proliferation of epithelioid and spindle-shaped melanocytes, in skin from the ear.
SECTION 5.0: SUPERFICIAL ATYPICAL MELANOCYTIC PROLIFERATIONS OF SPECIAL SITES

5.0.9

**Figure 5.0.9.2** The lesion is highly cellular and there is a prominent spindle cell component; however, the cells have variable from side to side across the lesion.

**Figure 5.0.9.3** The lesion is somewhat poorly circumscribed at its periphery. There is moderate (i.e., significant) actinic elastosis in the dermis.

**Figure 5.0.9.4** In this area the junctional component is highly cellular and there is confluence of nests. There is moderate to severe cytologic atypia in the form of nuclear enlargement, irregularity, and hyperchromatism. There is a junctional lesional cell mitosis in a junctional nest in the upper center portion of the image.

**Figure 5.0.9.5** A few cells protrude into the papillary dermis. There is a brisk infiltrative lymphocytic response.
Also, I do not believe this is a so-called special site nevus of the ear, because of the marked atypia as well as other attributes. Additional support for diagnosis of melanoma is provided by the presence of a few mitoses in the junctional component. In the dermis there is diffuse fibroplasia and a bandlike lymphocytic infiltrate in some areas, changes that are also more likely to be associated with melanoma than with nevi. I believe there is at least a focal area of invasion of the dermis and I would characterize this lesion as follows:

**DIAGNOSIS**

Skin of right ear: Malignant melanoma, superficial spreading type, with nontumorigenic and nonmitogenic invasive radial growth phase, nonulcerated, Clark’s level II, Breslow thickness 0.44 mm, apparently minimally excised, see Description and Comment.

**COMMENT**

The dermal mitotic rate in this lesion is zero (several junctional mitoses are present, but these are not significant prognostically, although useful diagnostically), tumor-infiltrating lymphocytes are nonbrisk to the focus of invasion (brisk elsewhere), there is an area where the epithelium is stripped; however, there is no underlying reaction so no definitive ulceration is present, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. Changes extend within less than 1 mm of peripheral specimen borders. There is no definitive evidence of an associated nevus, although some changes could be consistent with associated junctional melanocytic dysplasia. There is evidence of mild to moderate actinic elastosis in the adjacent dermis. Although I
am not qualified to comment on definitive surgical techniques for this lesion, it should clearly be completely excised with a margin of normal tissue, and I believe that arbitrary margins may be modified in the context of tissue preservation of important structures, depending on the overall circumstances (MPATH DX Category 4 or perhaps 3 depending on clinical preference). In this case, this lesion is clearly at low risk for distant metastasis but could have capacity for local persistence, recurrence, and progression if not excised.

**OVERALL COMMENT**

The ear is the single most common site for melanoma after correction for unit area, in men but not generally in women (11). However, this female patient has actinic elastosis indicating that her ear is a chronic solar damage (CSD) site. This greatly reduces the likelihood that her lesion is a special site nevus, in my opinion. In addition, the degree of cytologic atypia and architectural disorder, coupled with mitotic activity in this lesion are beyond that which can be accepted in a special site nevus, again in my opinion.
6.0 Superficial Atypical Melanocytic Proliferations in Congenital Nevi

6.0.1 A Congenital Lesion on the Foot of a Two-Year-Old Child
6.0.2 Congenital Nevus Versus Congenital Pattern Nevus With Dysplasia
6.0.3 Congenital Pattern Nevus With Atypia-Reactive Versus Dysplastic
6.0.4 Dysplastic Nevus Versus Melanoma Arising in a Nevus
6.0.5 Atypical Congenital Nevus Versus Melanoma
A congenital nevus is, of course, a melanocytic nevus that is present at birth, although this can present some problems of definition in older patients when maternal history or clinical documentation are not available. These lesions vary considerably in size, and many of them are much larger than common acquired nevi. Congenital nevi are typically classified as “giant” or garmentlike, “intermediate,” functionally defined as lesions that are amenable to excision with primary closure, and “small,” less than 2.5 cm in diameter. This size is, of course, large compared to most common acquired nevi.

Histologic observations of giant and intermediate congenital nevi indicate that they are usually characterized by extensive involvement of dermal and subcutaneous structures, including skin appendages. Some examples, however, are junctional. In a study of 87 congenital melanocytic nevi (CMN) of all sizes from infants 12 months of age or younger, the lesions were evaluated for depth of nevus cell involvement, overall epidermal and dermal pattern, and cytologic atypia (1). Most of the lesions involved the lower half of the reticular dermis, and about half infiltrated the subcutaneous tissue. The depth of nevus cell infiltration was positively correlated with the size of the lesion. The predominant dermal pattern was diffuse interstitial infiltration of the dermal or subcutaneous stroma. A more patchy distribution was associated with smaller lesions. Most of the lesions displayed no cytologic atypia, the presence of which was not associated with either size or location of the nevus.

Given that dermal involvement and skin appendage involvement are characteristic of congenital nevi, these features are considered to define a group of “congenital pattern nevi.” Clinical observations indicate that not all congenital pattern nevi are in fact truly congenital as defined by presence at birth. There is evidence that the significance of truly congenital nevi may be different in that they have different underlying genomic patterns. In a study of oncogene mutation patterns, congenital nevi tended to have a different oncogenic mutation pattern than acquired nevi, with more lesions having NRAS mutations than BRAF mutations. However, congenital pattern nevi that were not present at birth had predominantly BRAF mutations, similar to usual acquired nevi (2).

At least as viewed histologically, most large congenital nevi have no chronic solar damage (CSD) and therefore are “no CSD” lesions. Some may occur in chronically sun exposed sites; however, there may be a tendency to protect them from the sun, and in addition the pigment in these lesions presumably acts as ultraviolet barrier. In any event, one does not typically see severe solar elastosis in giant congenital nevi. Small congenital nevi may occur in chronically sun-exposed areas and may even be identified as incidental findings in melanoma reexcision specimens, associated with moderate or severe actinic elastosis. In addition, small congenital nevi may be precursors of melanoma, as discussed in the next paragraph.

A variety of atypical proliferations can occur in congenital nevi. Some of these are in the dermis and these may be benign as in cellular and/or proliferative nodules (3,4), or malignant as in dermal melanoma arising in a congenital nevus (5). Others arise, as is the case for most acquired melanomas, in the junctional component of the nevus. The incidence of melanoma in giant congenital nevi has been studied in registries and in populations and is of the order of less than 10% over a lifetime (1,6–8). A substantial fraction of these melanomas occur during childhood. The incidence of melanoma in intermediate congenital nevi is less certain; however, multiple cases have been reported (9). The incidence of melanoma in small congenital nevi was estimated by Rhodes (10). One or more histologic features of (mostly small) congenital nevi
were detected in about 8% of melanoma specimens, indicating a spatial association between melanomas and small congenital nevi. This observed frequency of histologic association was estimated to be greater than that expected on the basis of surface area by chance alone, suggesting that small congenital nevi might be precursors for at least some cases of cutaneous melanoma. That said, small congenital nevi and congenital pattern nevi are much more common in the community than melanomas, and it is not considered reasonable to attempt to prevent melanoma by excision of small congenital nevi.

Other atypical proliferations occur, probably more commonly, in the junctional component (8). Some of these may be the result of trauma and may therefore be reactive while others appear to represent examples of neoplastic progression. In evaluating the significance of these junctional proliferations, we generally apply criteria that are useful in de novo lesions that occur in normal skin. There are many examples of atypical junctional proliferations that are poorly described in the literature and are difficult to characterize with certainty, and in some of these cases a descriptive diagnosis of “superficial atypical melanocytic proliferation of uncertain significance” (SAMPUS) or “melanocytic tumor of uncertain malignant potential” (MELTUMP) may be the most appropriate (11).

From a clinical (and anecdotal) perspective, patterns resembling melanocytic dysplasia in congenital nevi often appear to be confined to the individual congenital nevus, rather than representing a more generalized tendency to develop dysplastic nevi. Therefore, their significance may be confined to the risk of future progression in that lesion itself, rather than as markers of increased risk for melanoma in other locations. Nevertheless, these lesions should serve as an indication for assessment of a patient’s melanoma risk factors, and especially if there are other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance may be appropriate.

References
6.0.1

A Congenital Lesion on the Foot of a Two-Year-Old Child

CLINICAL INFORMATION
Excision of a congenital nevus from a two-year-old child.

REASON FOR CONSULTATION
Sections show acral skin with junctional nevus, with extensive intraepidermal melanocytic proliferation. No mitotic activity is observed. The lesion appears closely excised. This case will be shown to dermatopathology and their conclusions and recommendations included as an addendum.

DESCRIPTION
These sections show a biopsy of skin, containing a very broad, moderately to highly cellular melanocytic proliferation in the epidermis, with a few nests in the upper dermis. The proliferation extends close to inked lateral borders but appears to be completely excised in the section planes available for study. The lesional cells are arranged in the epidermis as single cells and as nests, which tend to be relatively discrete and to be present mainly near the tips and sides of elongated rete ridges. Single cells are present in a lentiginous basal proliferation and also in a pagetoid scatter pattern, focally extending to the midspinous layer in some areas. Pagetoid scatter of nevus cells has been described in acral nevi, and therefore this may represent a so-called "special site" phenomenon in this case. In general, the lesional cells are nevoid to epithelioid, with relatively small nuclei, although in some areas...
FIGURES 6.0.1.2 and 6.0.1.3 There is an extensive junctional component that is variably cellular.

FIGURES 6.0.1.4 and 6.0.1.5 In some areas the proliferation is more cellular with pagetoid scatter of single cells and a tendency to confluence of nests along the junction; however, there is no extensive pagetoid scatter or continuous basal proliferation, severe uniform cytologic atypia, extensive mitotic activity.
the nuclei are somewhat larger with nucleoli. Mitotic figures are rare or absent. From reviewing the clinical record, it does not seem that this lesion has increased notably in size, although the mother had noted increased pigmentation of it. These changes present difficulties of interpretation because there are overlapping features with melanoma in situ. The findings will therefore be interpreted descriptively as follows:

**FIGURE 6.0.1.6** Melan-A staining appears to demonstrate continuous basal labeling; however, much of this is in dendrites and should be correlated with the hematoxylin and eosin sections in which most of the lesional cells are separated by keratinocytes.

**DIAGNOSIS**

Skin, left foot, excision of nevus: Lentiginous junctional nevus, congenital by history, with atypical features of uncertain significance, see Description and Comment.

**COMMENT**

These changes are difficult to interpret. Limited experience with congenital nevi in young patients, especially in the neonatal period, has identified markedly atypical junctional melanocytic proliferations, overlapping morphologically with melanoma in situ as seen in adults, yet followed over time by maturation to a more banal congenital nevus pattern. On the other hand, melanomas arising in congenital nevi have been described at all ages, including evolution in the junctional component. Based on the lack of severe cytologic atypia and mitotic activity, I would consider these changes to be most likely benign, reflecting a combination of congenital and “special site” features in the nevus. This particular nevus, although present at birth based on the history, does not show the typical “congenital pattern” features of involvement of the deep dermis and of skin appendages. Nevertheless, junctional or predominantly junctional congenital nevi have been described. It is reassuring that mitotic figures are absent in this lesion. As one additional test, it might be appropriate to perform a Ki-67 study to assess proliferation. If this is essentially negative it would be added evidence that this lesion is benign. If there are more than a few reactive cells, one might best regard this lesion as an example of a superficial melanocytic proliferation of...
uncertain significance (“SAMPUS”), with the caveat that evolving or early established melanoma in situ cannot be ruled out. I would consider this latter interpretation, however, to be quite unlikely because of the lack of dynamic changes (other than increased pigmentation) clinically, and the lack of mitotic activity. I would be most interested in reviewing additional biopsies from this lesion if it should become available, and/or clinical photographs.

**OVERALL COMMENT**

Although it is possible for melanoma to develop in congenital nevi even in this early age group, it is very rare and more often than not even the most atypical proliferations will follow a benign course. In a current case, I would order a p16 stain as well as a Ki-67 to assess cell cycle markers. Complete excision of this lesion would be appropriate management (MPATH DX Category 2).
6.0.2

Congenital Nevus Versus Congenital Pattern Nevus
With Dysplasia

**Clinical Information**
A lesion of the back in an 11-year-old boy.

**Reason for Consultation**
Is there significant atypia in this lesion?

**Figure 6.0.2.1**
A broad, generally symmetrical moderately cellular lesion, with a central elevated portion and junctional shoulders.

**Figures 6.0.2.2 and 6.0.2.3**
The lesion is well circumscribed at its periphery with the last cells in a nest. Nuclei are only mildly enlarged without marked hyperchromatism, irregularity, or nucleoli.
CASE 2: CONGENITAL NEVUS VERSUS CONGENITAL PATTERN NEVUS WITH DYSPLASIA

DESCRIPTION

These sections show a broad lesion characterized by orderly nevus cells in the papillary dermis, expanding it, and entering the reticular dermis at the base in a “congenital pattern.” In the overlying junctional component, there are some nests that bridge between adjacent elongated rete ridges, and there is some enlargement of nuclei with nucleoli. In the adjacent epidermis, there are similar changes, without marked nuclear enlargement or irregularity but with prominent nucleoli. Taking these findings together I would regard this lesion as a congenital pattern nevus. The adjacent junctional component has some dysplastic features; however, I would interpret this lesion descriptively as follows:

FIGURE 6.0.2.4 and 6.0.2.5 There is a dermal component comprised of nevoid melanocytes that show evidence of maturation from superficial to deep. The lesional cells enter the reticular dermis at the base in a so-called “congenital pattern.”

DIAGNOSIS

Skin, left upper back: Compound nevus with congenital pattern and mildly dysplastic features, completely excised, see Description and Comment.

COMMENT

Mild histologic dysplasia has been demonstrated in relatively recent case-control studies not to have independent significance as a risk factor for melanoma development (12,13) and especially in the context of mildly dysplastic features being seen adjacent to a congenital pattern nevus, and in a child I do not believe it necessarily has any significance. However, if this patient should have other clinically atypical nevi and/or a personal or family history of melanoma, consideration of additional assessment would be appropriate.
“Congenital pattern” nevi are so-called because many of them have been documented not to have been present at birth. These “tardive” congenital pattern nevi may have more features in common with acquired nevi than with truly congenital nevi. It is uncertain whether dysplastic changes in these lesions have the same significance as those in other nevi. In any event, mild dysplasia as seen in this lesion is not an independent risk factor for melanoma development in future life, and this lesion might equally well have been called “a compound nevus with congenital pattern features and lentiginous junctional component.” At the simplest level, it is a compound nevus. This is a benign lesion that would not necessarily require reexcision even if present at the specimen margins (MPATH DX Category 1).
6.0.3

Congenital Pattern Nevus With Atypia-Reactive Versus Dysplastic

**Clinical Information**
An irregularly pigmented lesion from the cheek of a 39-year-old woman.

**Reason For Consultation**
This was sent as a changing nevus. It is a compound nevus. The epidermal component displays some atypia of suprabasal melanocytes. I am concerned about the epidermis although not to the extent of calling it MIS.

**Figure 6.0.3.1** A relatively broad lesion characterized by nevus cells extending into the reticular dermis and around skin appendages in a congenital pattern. There is an atypical superficial proliferation that is sparsely to moderately cellular but irregularly distributed across the lesion.

**Figures 6.0.3.2 and 6.0.3.3** There is fibroplasia in the superficial dermis above the dermal nevus cells. There are increased single cells in the epidermis.
These sections show a shave biopsy of skin containing the top of a lesion characterized by an orderly dermal nevus component that extends around skin appendages and is focally neurotized, consistent with a congenital pattern nevus. In the overlying epidermis toward the center of the lesion but not extending beyond its periphery, there is a somewhat atypical intraepidermal proliferation of nevoid to epithelioid melanocytes, with some moderate nuclear size, shape, and staining variation but without extensive continuous basal proliferation, and without mitotic activity. The significance of these findings is uncertain and one might consider mild to moderate dysplasia; however, there is some evidence of fibroplasia in the upper dermis in this area and I also considered the possibility that these relatively minor changes could be ascribed to prior trauma. In summary, I would interpret this lesion descriptively as follows:

**FIGURES 6.0.3.4 and 6.0.3.5** There is mild to moderate atypia of lesional cell nuclei in the epidermis; however, there is no extensive continuous basal proliferation or high-level pagetoid scatter, no high-grade atypia, no mitotic activity, and in short no evidence of melanoma.
**Case 3: Congenital Pattern Nevus with Atypia - Reactive versus Dysplastic**

**Diagnosis**

Skin, cheek: Compound nevus with congenital pattern features, and focal atypia of the junctional component, see Description and Comment.

**Comment**

As noted above, I believe that the atypia may well be reactive or at worst could be considered moderately dysplastic. Consideration of complete excision would be appropriate for this lesion (MPATH DX Category 2).

**Overall Comment**

The significance of melanocytic dysplasia in a congenital pattern nevus may be an isolated phenomenon in my experience; however, if this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, additional evaluation and possible surveillance might be indicated. In any case, this lesion has minimal features of dysplasia at worst and the changes are most likely reactive, possibly to trauma.
6.0.4

Dysplastic Nevus Versus Melanoma Arising in a Nevus

**Clinical Information**
An irregular variegated pigmented lesion on the back of a 53-year-old man.

**Reason for Consultation**
Sections show a quite broad, compound melanocytic lesion that is characterized by an irregular increase in the density of nonnested junctional melanocytes, focal junctional melanocyte nesting, fibrosis and inflammation of the superficial dermis, and dermal melanocyte. This lesion exhibits atypical features including confluent lentiginous melanocytic proliferation, scattered melanocytes above the dermal–epidermal junction, and moderate to severe cytologic atypia for both junctional and some of the dermal melanocytes, which are weakly stained with HMB 45. Ki-67 staining of intradermal melanocytes is focally increased. Cytologically bland dermal melanocytes are also noted. Most of the melanocytes are cytoplasmicly positive for p16. The lesion extends close to the lateral margin of this specimen and may involve the lateral margin. The differential diagnosis could include a severely atypical dysplastic nevus versus a malignant melanoma arising in a nevus. Given the broad lesion, cytologic atypia, and patient history of melanomas, this lesion is being sent to a consultant for a second opinion.

**Description**
These sections show an excision biopsy of skin, containing a moderately to focally more highly cellular proliferation of nevoid to epithelioid melanocytes, arranged singly and in nests with nests generally predominating, near the dermal–epidermal junction, and with many nests bridging between adjacent elongated rete ridges especially at the periphery of the lesion. A few lesional cells rise above the junction in a pagetoid scatter pattern that is quite extensive across the lesion but generally does not

**Figure 6.0.4.1** A broad, superficial lesion with a somewhat asymmetrical silhouette.
FIGURE 6.0.4.2 There are nests in the epidermis that vary in distribution.

FIGURE 6.0.4.3 There is a peculiar pattern of single nevoid melanocytes extending into the dermis in a fibrous stroma. These have bland nuclei and show evidence of maturation from superficial to deep.

FIGURE 6.0.4.4 Superficially there are larger nests in the dermis, comprised of cells with uniform moderate atypia characterized by slight nuclear irregularity and hyperchromatism, and small nucleoli.

FIGURE 6.0.4.5 Lesional cells in junctional nests tend to become confluent, and similar cells in the papillary dermis are associated with diffuse fibroplasia and limited evidence of maturation. There is also pagetoid scatter of single cells in the epidermis although not beyond the lower third.

extend upward beyond the midspinous layer. Toward the center of the lesion, there is some tendency to confluence of nests in the epidermis, and similar cells to those in the epidermis are present in the papillary dermis and upper reticular dermis, generally showing evidence of maturation along nevic lines. Some small clusters of lesional cells located superficially in the dermis show lesser evidence of maturation and
6.0.4

they have somewhat enlarged nuclei, some with nucleoli. After prolonged searching, a single lesional cell mitosis is identified in the superficial dermis (not shown). Ki-67 staining demonstrates only a few reactive cells in the dermal component. Taken together, these findings are concerning; however, I believe they do not justify an unequivocal diagnosis of melanoma and I would interpret this lesion descriptively as follows:

**DIAGNOSIS**

Skin, left midback: Compound nevus with congenital pattern features and severe dermal and epidermal dysplasia, apparently excised, see Description and Comment.

**COMMENT**

Although I believe these findings are not diagnostic of melanoma, the presence of a dermal mitotic figure in association with cytologic atypia is quite concerning for the possibility of a melanoma, which, in a “worst-case scenario,” would be nonulcerated and would have early tumorigenic but nonmitogenic vertical growth phase, at a greatest Breslow thickness of approximately 0.5 mm, as measured to somewhat immature cells in the slide containing a mitosis. The dermal mitotic rate would be 1/mm², tumor-infiltrating lymphocytes would be sparse, there is no radial growth phase regression, no microscopic satellites, and no evidence of vascular, lymphatic, or neural invasion. There is evidence of an associated compound dysplastic nevus with congenital pattern features and there is moderate actinic elastosis in the dermis. The lesion is excised in the section planes available for study with a closest margin of 1 mm. I would recommend consideration of management with the above differential diagnosis taken into consideration, and although this might include consideration of an additional excision procedure and sentinel node staging, I do not believe these procedures, although reasonable to consider, are necessarily standard of care in a completely excised borderline lesion of this type. (MPATH DX Category 3 or 4, depending on clinicopathologic circumstances and patient and physician preference.)

**OVERALL COMMENT**

In general, as a rule of thumb, I believe that mitotic activity in an equivocal or “borderline” lesion such as this tips the balance in favor of a diagnosis of melanoma; however, in this case I believe that other sufficient criteria are lacking. On the other hand, this degree of atypia in a somewhat older individual is at least somewhat concerning and warrants complete excision of this lesion. Also, if this patient should have other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance may be appropriate.
6.0.5

Atypical Congenital Nevus Versus Melanoma

CLINICAL INFORMATION
A congenital pigmented lesion present at birth presenting for evaluation in a six-month-old infant. The lesion was described as very dark with nodular components. It is not clear whether the lesion has been changing recently.

REASON FOR CONSULTATION
I am concerned about the severe atypia in this lesion.

DESCRIPTION
These sections show multiple section planes of a highly cellular proliferation of nevoid, spindled, and epithelioid melanocytes, from a lesion stated to be a congenital nevus, which was very dark with nodular components, in a 7.5-month-old infant. I assume from the history that this lesion was truly congenital. It is comprised of quite variable lesional melanocytes, ranging from relatively small nevoid cells to large epithelioid cells, and from amelanotic to heavily pigmented cells. Across the junctional component, there is quite striking pagetoid scatter of epithelioid melanocytes into the epidermis extending to the stratum corneum in some areas. There is no ulceration, but in one of the sections there is a scale-crust. Large epithelioid melanocytes protrude from near the epidermis into the papillary dermis and infiltrate the upper reticular dermis to a depth of 0.95 mm. These have abundant cytoplasm with moderate amounts of finely divided “dusty” melanin pigment. Their nuclei are relatively large, somewhat irregular, and somewhat hyperchromatic. Some of them have prominent nucleoli. Scattered mitotic figures are readily

FIGURE 6.0.5.1 A broad, rather asymmetrical lesion in skin of a six-month-old child.
FIGURE 6.0.5.2 At one periphery of the lesion, there are single cells and nests arranged mainly near the dermal–epidermal junction. There is some pagetoid scatter generally not beyond the lower third. In the dermis, there are patchy lymphocytes and melanophages. There is no cytologic atypia in this area of the lesion.

FIGURE 6.0.5.3 Toward the center of the lesion, the cytology changes and the lesion is comprised of large epithelioid cells with abundant cytoplasm.

FIGURE 6.0.5.4 The cells tend to have large nuclei with regular nuclear membranes, pale chromatin, and prominent nucleoli. This cytology could be considered “Spitzoid.”

FIGURE 6.0.5.5 There is some evidence of maturation from superficial to deep in that the nuclei of the cells become smaller; however, the cytoplasm remains abundant and there is finely divided cytoplasmic melanin pigment. Mitotic figures are rare or absent.
identified, but the mitotic rate overall is low at 1/mm². Significantly, there is a suggestion of maturation of the cells from larger cells in the epidermis to the epithelioid cells in the dermis, to a somewhat smaller nevoid to epithelioid cell type at the base of the tumor in the reticular dermis. In the dermis also, one can identify mature nevus cells in the reticular dermis and around skin appendages beneath the atypical superficial component. These findings are consistent with the history of this nevus being congenital. Given the extremely young age of this infant, I do not believe these changes can be interpreted as melanoma despite the severe atypia, both architectural and cytologic. Alarming cellular and proliferative lesions can occur in congenital nevi in infancy and be followed by a benign course. On the other side of the question, melanomas
6.0.5

in this age group are exceedingly rare although not unheard of, especially in this context of a congenital nevus. I would therefore interpret this specimen descriptively as follows.

**COMMENT**

**COMMENT 1**

As briefly discussed above, melanocytic tumors occurring in infancy cannot be considered using the same criteria as those in adults. Although this lesion has many features of melanoma of the superficial spreading type as seen in adults, I do not believe these changes have the same significance in this context. One might consider the possibility of an unusual cellular and proliferative nodule occurring in a congenital nevus, although most of these lesions do not have the striking pagetoid scatter seen over a broad front in this particular case. There are also spitzoid cytologic features as noted above. In my opinion, this lesion will most likely have a benign course. However, there is obviously some uncertainty given the dermal atypia, tumorigenic proliferation, and mitotic activity in this lesion. To assist in this interpretation, I will order a couple of additional immunostains, in addition to your Ki-67, which is useful in showing a low proliferation rate in the dermal component with most of the positive cells being in the upper third of the lesion. HMB 45 can be somewhat useful to assess differentiation and p16 is useful to assess for the absence or possible presence of chromosome 9p21 loss, which is the only genomic marker that has been convincingly shown to be associated with aggressive behavior in problematical melanocytic tumors, including mostly atypical spitzoid lesions. If p16 is present then 9p21 loss cannot have occurred. If the p16 antigen is present in one of the characteristic patterns of benign nevi, namely either a checkerboard pattern or a diffuse pattern, then this can be to some extent reassuring. In any event, although this lesion appears completely excised, changes extend within less than 1 mm of specimen borders. One might consider an additional procedure, especially if there is any doubt about the excision of this lesion, or alternatively careful follow-up of the lesional site. Attention to regional lymph nodes as a baseline would, of course, also be appropriate. I do not believe sentinel node staging is a standard of care for lesions of this type, although possibly reasonable to consider. We will order special stains as mentioned above and report on the results in a few days.

**COMMENT 2 (A FEW DAYS LATER)**

HMB 45 and p16 stains and also an additional H&E stain have been reviewed. HMB 45 stains the immature populations of cells quite brightly, especially superficially, and in some areas the staining extends to the base while in other areas the deeper cells stain less intensely, representing a “top-heavy” pattern, which in general is reassuring with focal areas that are more concerning. The p16 immunostain, reassuringly, stains these areas of HMB 45 staining and other regions of involvement by the large atypical epithelioid cell type. As discussed above, this indicates that 9p21 loss cannot have occurred in this lesion. Furthermore, the staining patterns are either diffuse or “checkerboard,” including nuclear staining, patterns that have been associated with benign lesions. Although I do not regard these findings as definitive, I do regard them as reassuring and consistent with literature that has found atypical proliferations in congenital nevi, especially those in very young children, to more often than not behave in a benign fashion. I would therefore, as discussed above, recommend a complete surgical elimination of this lesion, or at least of the atypical proliferative foci, which I believe has been done. I would also recommend careful follow-up for
this young patient with attention to regional lymph nodes. However, I do not believe that sentinel node staging is standard of care in these lesions. Although one could consider fluorescence in situ hybridization for this lesion (14), given the presence of p16 staining, which rules out 9p21 loss, I'm not sure that this technique has much to offer in terms of adding to the prognostic information.

In our experience, even markedly atypical proliferations present in congenital nevi in neonates and very young infants have followed a benign course. That said, complete excision of the atypical proliferation would be appropriate if possible (MPATH DX Category 2 or 3).
7.0 Superficial Proliferations of Spindle and/or Epithelioid Melanocytes

7.1 Superficial Pagetoid and Atypical Spitzoid Proliferations
   7.1.1 Atypical Pagetoid Spitz Tumor Versus Spitzoid Melanoma
   7.1.2 Atypical Spitz Tumor Versus Pagetoid Melanoma
   7.1.3 Atypical Spitz Tumor Versus Spitzoid Melanoma
   7.1.4 Melanocytic Tumor of Uncertain Malignant Potential, Atypical Spitz Tumor Versus Spitzoid Melanoma
   7.1.5 Melanocytic Tumor of Uncertain Malignant Potential, Favor Atypical Spitz Tumor Versus Favor Spitzoid Melanoma
   7.1.6 Pagetoid Spitz Tumor Versus Superficial Spreading Melanoma

7.2 Pigmented Spindle Cell Nevi
   7.2.1 Pigmented Spindle Cell Nevus Versus Pagetoid Spitz Versus Superficial Spreading Melanoma
   7.2.2 Atypical Pigmented Spindle Cell Nevus Versus Superficial Spreading Melanoma Versus Severely Dysplastic Nevus
   7.2.3 Pigmented Spindle Cell Nevus Versus Severe Dysplasia or Evolving Melanoma In Situ
   7.2.4 Pigmented Spindle Cell Nevus Versus Pigmented Spitz Nevus Versus Severely Dysplastic Nevus
   7.2.5 Superficial Atypical Melanocytic Proliferation of Uncertain Significance, Pigmented Spindle Cell Nevus Versus Spindle Cell Melanoma
Melanocytic tumors comprised of “large spindle and/or epithelioid melanocytes” have been divided into two major categories, named after Sophie Spitz (1) and Richard Reed (2) respectively. Some may consider the Reed nevus to be simply a pigmented variant of the Spitz nevus. However, we believe there are reproducible morphological differences, and these lead to different diagnostic considerations. The Reed nevus, for example, is more likely to be misdiagnosed as superficial spreading melanoma, while the Spitz nevus/tumor is more likely to be misdiagnosed as nodular melanoma.

It could also be argued that these are simply variants of common acquired nevi. However, recent studies by Bastian and colleagues have identified significant genomic differences between the categories of common nevi and Spitz nevi/tumors (3). It has been found that a large fraction of Spitz tumors have gene fusions that drive their proliferation rather than activating mutations of single oncogenes as is usually the case in common acquired nevi and indeed also in congenital nevi. Therefore, it seems reasonable to consider these as a special class of lesions. Because of differences between Spitz lesions and ordinary nevi, it has been suggested that they should be referred to as “tumors” or “melanocytomas” (4), terms which perhaps better capture their sometimes unpredictable biology.

Spitz nevi/tumors and pigmented spindle cell nevi (PSCN) tend to occur in a younger age group than melanomas, and are not usually associated with severe chronic solar damage (CSD). It is possible that these lesions may be seen in skin with mild or moderate actinic elastosis; however, in our opinion the diagnosis of either of these conditions should be made with caution in skin that shows significant actinic elastosis and in older age groups. That said, relatively characteristic examples of each of these conditions can be seen in older individuals, certainly into the seventh decade. Nevertheless, age remains an important consideration in the diagnosis of Spitz tumors, and an atypical Spitzoid lesion in an older subject should generally be managed as a melanocytic tumor of uncertain malignant potential, with at least a complete excision procedure and a consideration of follow-up.
The lesion described by Sophie Spitz in 1948 as “melanoma of childhood” (1) has undergone considerable changes in concept and in terminology. One of the lesions she described was in fact a fatal melanoma; however, the prognosis of most of the cases was excellent despite morphology considerably resembling that of melanoma. The lesions were therefore generally thereafter referred to as “Spitz nevi,” and more recently as “Spitz tumors.”

The typical Spitz nevus occurs in a child, often on the face, as a pink papule, which appears, reaches a relatively small size, and stops growing. Histologically, Ackerman’s term “nevus of large spindle and/or epithelioid melanocytes” aptly describes the lesions (5). The lesions are symmetrical both in terms of their architecture and in terms of their cytology, with lesional cells looking the same from side to side at any level but showing evidence of maturation from superficial to deep within the dermis. The lesional cells of Spitz nevi/tumors are large and/or spindled in configuration and have abundant amphophilic cytoplasm, and large nuclei, which are ovoid or round, with irregular nuclear membranes, pale chromatin, and prominent often eosinophilic nucleoli. These cytologic features are the primary defining and diagnostic criteria for Spitz tumors. A curious feature in the junctional component is the presence of globoid eosinophilic bodies called “Kamino bodies” after their describer (6). These have been demonstrated to represent basement membranelike material (7,8). They are only very rarely seen in metastasizing melanomas. Mitotic figures are rare or absent in typical Spitz nevi. Most of these lesions, although small, extend into the reticular dermis to thickness of greater than 1 mm. The smaller cells at the base typically disperse into the reticular dermis as single cells, reflecting inability to infiltrate and survive in the reticular dermis, but not to divide to form nests or fascicles of cells.

The relationship between Spitz nevi/tumors and ordinary nevi and melanomas has been debated. The Spitz lesions have highly characteristic cytologic features. It has recently been demonstrated that they also have characteristic genomic profiles, being for the most part associated with fusion genes forming constitutively active chimeric oncogenes as drivers rather than retaining oncogenes as is more typical for nevi and melanomas (3). This finding supports the practice of regarding these lesions as different from usual nevi and melanomas, which is important for management and for prognosis.

Lesions with variations on the classical architecture and cytology have been identified, often in an older age group. These in general have been termed “atypical Spitz nevi” or, more currently, “atypical Spitz tumor (AST),” to reflect a somewhat uncertain biology (4). The term “melanocytoma” has been advocated for this reason (9), or the lesions have been designated as Spitz “nevus/tumor” (4). Atypical features in Spitz tumors include larger size, poor circumscription, asymmetry, consumption or thinning of the epidermis, ulceration, pagetoid scatter into the epidermis, failure of maturation in the dermis,
greater degrees of atypia than is usual, and increased mitotic activity. In a comparative study of Spitzoid melanomas and Spitz nevi, six features had significant distinguishing capacity (10): (1) Kamino bodies, (2) a brisk mitotic rate, (3) mitoses close to the base of the lesion, (4) abnormal mitoses, (5) symmetry, and (6) uniformity of nests from side to side.

In another study of 75 AST, 21 of which had metastasized regionally and three of which had metastasized systemically and caused death, interobserver agreement and use of criteria among 13 expert dermatopathologists were studied. There was low interobserver agreement for the categorization of the lesions as malignant versus nonmalignant. Histologic features given the most diagnostic weight by the experts were consumption of the epidermis, atypical mitoses, high-grade cytologic atypia, and mitotic rate. In contrast, the histologic features that correlated best with disease progression were frequent mitoses, deep mitoses, asymmetry, high-grade cytologic atypia, and ulceration. Pagetoid spread, consumption of the epidermis, and lymphoid aggregates were not correlated with behavior. These were bulky tumors, none of which would fit into the general category of “superficial atypical melanocytic proliferations” under consideration in this section. These results demonstrate a lack of consensus in the assessment of ASTs, and also a lack of correlation of many features used in establishing this diagnosis with outcome (11).

When an insufficient number of these atypical criteria is present for a definitive diagnosis of malignancy, and yet melanoma cannot be ruled out, the lesions may appropriately be referred to as “melanocytic tumors of uncertain malignant potential (MELTUMP)” (9). The term “Spitz tumor of uncertain malignant potential” or “STUMP” has also been used in this context (12). Agreement as to these diagnostic categorizations is often elusive (13). In the past, sentinel node staging was offered to patients with AST, and when this was positive, the diagnosis was often revised to “malignant melanoma” or “Spitzoid melanoma.” Multiple studies over the last several years, however, have demonstrated that although sentinel node metastasis occurs in about a third of atypical Spitzoid lesions in which this procedure is performed, the positive finding does not predict a fatal outcome, with essentially no reported deaths having occurred in more than 100 reported cases (14–23).

In this section we concentrate mainly on superficial examples of Spitz tumors, especially those with atypical features, one of the commonest of which is the presence of marked pagetoid scatter into the epidermis. In addition, we will discuss examples of Spitzoid lesions that are predominantly in situ or that have a junctional component that extends beyond the dermal component, which in the early usage was considered to be an atypical finding, or even a finding to exclude the diagnosis of a Spitz lesion. These lesions present architectural features, such as shoulder formation and bridging nests that overlap with those of dysplastic nevi, but have cytological features of Spitz lesions (24).

Although in general pagetoid scatter into the epidermis is a criterion that has traditionally raised suspicion for melanoma, there are examples of unquestioned Spitzoid proliferations that have prominent scatter of lesional cells into the epidermis. In a comprehensive study by Requena (25), pagetoid scatter was seen in 13% of 349 Spitz tumors. This phenomenon was mentioned in earlier descriptions but first clearly described by Busam in 1995 (26). He emphasized that these lesions typically presented clinically as a small, less than 4 mm in diameter, pigmented macule in a young patient. Some lesions may present as a pigmented or nonpigmented (pink) plaque or dome-like lesion. As with other Spitz tumors, there is often a history of recent appearance followed by
stability. Busam emphasized that histologic features favoring nevus over melanoma include smaller size, circumscription, symmetry, a uniform distribution of cells, and the lack of marked cytologic atypia.

The diagnostic distinction of pagetoid and other atypical Spitzoid proliferations from melanoma can be very challenging, especially in older individuals. Gerami and colleagues found in a study of superficial melanocytic neoplasms with pagetoid melanocytosis that fluorescence in situ hybridization (FISH), using a four probe set, accurately identified as malignant five of seven cases, which had a consensus diagnosis of melanoma (27). In a later study of atypical Spitzoid proliferations, although not focused on those with pagetoid melanocytosis, it was found that homozygous loss of chromosomal location 9p21 was associated with those rare cases that exhibited aggressive behavior (28). This is the chromosomal locus of cyclin-dependent kinase inhibitor (CDKN) 2A, the gene encoding the tumor suppressor p16, as well as other tumor suppressors (e.g., CDKN2B or p15) and other genes (29). We therefore consider that immunohistochemical staining for p16 may be useful in ruling out the possibility of 9p21 loss in an atypical Spitzoid proliferation.

Other markers that may be helpful in atypical Spitzoid proliferations include the proliferation marker Ki-67, and HMB 45 which may be viewed as a marker of “maturation.” A low proliferation rate with Ki-67, a “top-heavy” pattern with HMB 45 (30), and expression of p16 (31–36) are reassuring features in atypical Spitzoid proliferations. The p16 protein can be expressed in melanomas so is not a perfect marker for a benign lesion. However, two patterns of expression, namely a “checkerboard” pattern in which about 50% of the cells are stained in a characteristic pattern, or a diffuse cytoplasmic and nuclear staining pattern, seem to be characteristic of benign lesions and are reassuring when present (31).

As discussed above, in terms of the etiology/site/CSD classification of melanocytic lesions, Spitz tumors including ASTs and most Spitzoid melanomas are either “no CSD” or “low CSD” lesions. In our opinion, the diagnosis of an AST should be made with great circumspection in the presence of moderate or severe CSD.

In summary, superficial atypical Spitzoid proliferations can present diagnostic difficulties in the distinction from severe melanocytic dysplasia, which could have significance as a marker of an individual at increased risk for melanoma, and malignant melanoma, especially that of the superficial spreading type in its radial growth phase. In contrast, Spitzoid proliferations, even atypical ones, do not have any significance as risk markers or as potentially aggressive and lethal tumors, with only rare exceptions. Identifying these rare exceptions is, of course, important, and difficult.

**GENERAL MANAGEMENT PRINCIPLES FOR SPITZ NEVI/TUMORS**

Some experienced physicians make a distinction between lesions they term “Spitz nevi,” which are small symmetrical lesions in young children lacking atypical features, and “Spitz tumors,” which tend to be larger and in older individuals, and may present varying degrees of architectural and cytologic atypia. In such a distinction, the small lesions in young children may be managed as other nevi, with biopsy being done only as necessary to rule out any remote possibility of malignancy in a clinically atypical lesion. It may well be appropriate to follow many of these lesions as a part of routine pediatric care. Incompletely excised examples of these small lesions could potentially be followed in the same manner. However, if the lesion had been removed because of clinical concerns, then complete excision would likely be judicious. Therefore, these lesions are MPATH DX Category 1 or 2 lesions.
Larger lesions for which the term “Spitz tumor” may be more appropriate, and lesions with atypical features (ASTs) should be excised completely with clear margins, both to be sure the lesion has been completely examined histologically, and also hopefully to preclude any remote possibility of persistence, recurrence, or progression of the lesions (MPATH DX Category 2). Although such progression is generally very rare indeed, we have seen examples of lesions that have recurred at a local site, sometimes with increased atypia, which has led to concern for the possibility of recurrent melanoma and could certainly lead to overdiagnosis if the prior history and biology are not well understood.

In lesions termed “Spitzoid melanomas,” as discussed above, most treating physicians would choose to manage the lesion as a melanoma, namely MPATH DX Category 3 or 4. It is not clear that microstaging attributes developed for usual forms of melanoma are predictive of biology in these lesions. The question of sentinel node staging has been discussed above and is a difficult issue. Many studies have found that positive sentinel nodes are not uncommon in ASTs or Spitzoid melanomas; however, this finding does not predict aggressive behavior and the survival in a relatively large number of reported cases, at least in younger age groups, has been literally 100%. Therefore, while reasonable to consider, sentinel node staging is not standard of care for these unusual lesions in our opinion. Staining for p16, followed if indicated by FISH and comparative genomic hybridization (CGH) can in our opinion be helpful in making decisions regarding management, and in a lesion with 9p21 homozygous loss we would recommend consideration of management as for a usual form of melanoma, taking its microstaging parameters into full consideration.

**References**

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7.1.1

Atypical Pagetoid Spitz Tumor Versus Spitzoid Melanoma

**Clinical Information**
A pink plaque that appeared recently on the left shin of a 4-year-old child.

**Reason for Consultation**
Is this a benign Spitz tumor? Should it be reexcised? Should a sentinel node staging procedure be done?

**Figure 7.1.1.1** A broad, plaquelike, moderately to highly cellular proliferation in the dermis and in the papillary dermis.

**Figure 7.1.1.2** At one periphery the lesion is well circumscribed with the last cells being present in the form of a nest.

**Figure 7.1.1.3**
DESCRIPTION

These sections show a shave biopsy of skin, containing a moderately to highly cellular, predominantly junctional proliferation of large spindle and/or epithelioid cells, forming a rather well-circumscribed lesion that measures about 5 mm in diameter on the slide. The lesional cells are arranged in nests near the dermal–epidermal junction, some with prominent clefting artifact. There are also single cells, many of which extend up into the epidermis in a pagetoid scatter pattern to the stratum corneum focally. The cells contain moderate amounts of melanin pigment in the form of relatively finely divided granules. There are a few globoid eosinophilic Kamino bodies present at the interface. Similar cells protrude into the papillary dermis and upper reticular...

FIGURE 7.1.1.4

FIGURES 7.1.1.3 and 7.1.1.4 Toward the center there are prominent globoid eosinophilic (dull pink) Kamino bodies. The lesional cells are large, spindled and/or epithelioid, with large nuclei, regular nuclear membranes, pale chromatin, and prominent nucleoli. Mitotic figures are rare or absent.

FIGURE 7.1.1.5

Toward the base, the cells in this case show little evidence of maturation to a smaller cell type or dispersion as single cells into the reticular dermis.

FIGURE 7.1.1.6

Dermal lesional cells stain strongly, indicating a lack of the “top-heavy” pattern of HMB 45 staining that is indicative of maturation and when present is a reassuring finding in Spitz tumors.

FIGURES 7.1.1.6 and 7.1.1.7 An HMB 45 stain demonstrates prominent pagetoid scatter into the epidermis. Dermal lesional cells stain strongly, indicating a lack of the “top-heavy” pattern of HMB 45 staining that is indicative of maturation and when present is a reassuring finding in Spitz tumors.
dermis, some showing some evidence of maturation along nevic lines, with a few cells dispersing as single cells into reticular dermis collagen, to a Breslow thickness of approximately 0.6 mm. Dermal mitotic figures are rare or absent. There is a rare mitotic figure in the junctional component and there is only a rare Ki-67 positive cell in the dermal component. HMB 45 stains dermal cells without any evidence of a “top-heavy” pattern, an atypical feature. Taking these findings together, and also into consideration the age of the patient, I believe that it is best classified as a spindle and epithelioid cell melanocytoma of the Spitz type, with atypical features that I would characterize as follows:

**COMMENT**

In the context of the patient in this age group I believe these appearances are consistent with a so-called pagetoid Spitz nevus or “melanocytoma.” Given the rather minimal dermal component and lack of mitotic activity, I would not expect this lesion to have competence for metastasis. The lesion appears to be completely excised in two profiles available for evaluation; however, if there were any doubt about the excision clinically I would recommend an additional procedure to be sure this rather unusual lesion has been completely removed for complete histologic evaluation and, in any case, periodic follow-up of the lesional site would be appropriate.

**OVERALL COMMENT**

Despite the atypical features in this lesion, in the context of a child in this very young age group, the obvious Spitzoid cytology of this lesion, the presence of Kamino bodies, and the low mitotic rate, we would not expect any aggressive behavior from this lesion. If this lesion were on the specimen margin, we would recommend consideration of an additional procedure to be sure it has been completely removed, or perhaps in this context of a young child, careful follow-up of the lesional site (MPATH DX Category 1 or 2).
Atypical Spitz Tumor Versus Pagetoid Melanoma

**Clinical Information**
A pigmented lesion of the right upper arm in a 20-year-old woman, which appeared within the last few months.

**Reason for Consultation**

**Description**
These sections show a shave biopsy containing a highly cellular proliferation of uniformly large spindle and/or epithelioid melanocytes arranged in nests that tend to be quite large and vertically oriented mainly along the tips and sides of elongated rete ridges.

In addition, there are single cells, many of which extend up into the epidermis in a pattern of pagetoid scatter to the stratum corneum quite extensively across the lesion. Also at the junction there are prominent eosinophilic Kamino bodies. The lesional cells have moderately abundant cytoplasm and large nuclei with regular nuclear membranes, pale chromatin, and prominent nucleoli. Some of them contain moderate amounts of melanin pigment. In summary,
7.1.2

**FIGURE 7.1.2.3** At one periphery, the lesion is well circumscripted with the last cells present in the form of a nest.

**FIGURE 7.1.2.4** The lesion is comprised of large spindle and/or epithelioid cells, which are uniform from side to side across the lesion.

**FIGURE 7.1.2.5** A globoid dull pink Kamino body is seen at the dermal–epidermal junction in this and the previous figure.

**FIGURE 7.1.2.6** A few cells in the dermis at the base of the lesion show some evidence of maturation along nevic lines.

These are changes of a spindle and epithelioid cell melanocytoma with features of classic Spitz and pigmented spindle cell types, which I would characterize as follows:
As noted above, this lesion cytologically qualifies as a spindle and epithelioid cell melanocytoma with features of classic Spitz and pigmented spindle cell nevus. The prominent pagetoid scatter may be seen in so-called “pagetoid Spitz nevi,” which are most often seen in young individuals. This is, of course, an atypical feature as is the presence of a somewhat immature dermal component; however, there is no extensive expansile proliferation or mitotic activity in the dermis. I would therefore expect this lesion to be benign. Because it extends to specimen margins and because we have seen recurrences of Spitzoid lesions, sometimes with increased atypia, I would recommend an additional procedure to be sure this lesion has been completely removed (MPATH DX Category 2).

**OVERALL COMMENT**

There is overlap between spindle and/or epithelioid cell melanocytic tumors of the classic Spitz type and the pigmented spindle cell nevus of Reed. In this particular case, the narrow elongated spindle cells and the lack of clefting artifact are features more characteristic of pigmented spindle cell nevus, while the lack of pigment in the Kamino body are features more characteristic of classic Spitz lesions. The clinical significance of the two diagnoses are the same; however, the existence of differences between classic examples of each lesion indicates that it is reasonable to maintain them as separate although related entities.
CLINICAL INFORMATION
Lesion on the left thigh of a 39-year-old female, described as a 4 mm pink papule.

REASON FOR CONSULTATION
I favor the diagnosis of an AST over an unusual form of melanoma with Spitzoid features, but I am hesitant to make a conclusive diagnosis because of the age of the patient.

DESCRIPTION
These sections show a shave biopsy of skin containing a relatively broad, symmetrical lesion comprised of a highly cellular junctional and a moderately to focally more highly cellular dermal component comprised of large spindle and/or epithelioid melanocytes. These cells are arranged predominantly in nests along the dermal–epidermal junction, some with prominent clefting artifact. Numerous pink eosinophilic, relatively poorly developed Kamino-like bodies are observed. The epidermis is generally hyperplastic, but there is a focal area of thinning or “consumption.” Lesional cells descend into the papillary dermis showing only slight...

7.1.3

FIGURE 7.1.3.3
FIGURE 7.1.3.4 The lesion is comprised of uniform population of spindle cells. Ill-defined eosinophilic “Kamino bodies” are present superficially.

FIGURE 7.1.3.5 Cells at the base show only slight if any evidence of maturation and no dispersion into the reticular dermis. A mitotic figure is present, indicated by the arrow.

evidence of maturation along nevic lines, and without dispersing into the reticular dermis collagen. Mitotic figures are relatively frequent in the junctional component, and a rare mitosis is present in the dermal component, including in its lower third. There is a brisk infiltrative lymphocytic response across the base. The lesion is located in skin with moderate actinic elastosis. Taken together, I would consider that these criteria are consistent with a spindle and epithelioid cell melanocytic tumor of the Spitz type, with atypical features, including the failure of maturation and a focal area of somewhat greater cellularity of the dermal component, with focal consumption of the epidermis, the age of the patient, and the location in chronically sun-damaged skin. I do not believe these changes are sufficient for diagnosis of melanoma or Spitzoid melanoma, and I would therefore characterize this lesion as follows:
COMMENT

It is usual to recommend complete excision of Spitz tumors and in this case even though the margin is close but clear I would recommend consideration of an additional procedure to be sure this lesion has been completely removed (MPATH DX Category 2). The differential diagnosis could include a melanocytic dysplastic or other neoplastic process; however, I do not favor this interpretation. Nevertheless, especially given this patient’s age, it would be judicious to assess her other melanoma risk factors, and especially if there are other clinically atypical nevi and/or a family or personal history of melanoma, periodic surveillance of her skin may be appropriate.

OVERALL COMMENT

The high cellularity of this lesion, especially in its dermal component is somewhat concerning; however, the presence of Kamino bodies is reassuring and the cytology is consistent with a Spitz tumor. The paucity of dermal mitotic activity is reassuring. In my current practice, I would perform immunostaining for HMB 45 (expecting a “top-heavy” staining pattern), Ki-67 (expecting minimal staining of the dermal component), and p16 (expecting to see nuclear and cytoplasmic expression in the atypical lesional cells), and if the results of these were reassuring I would consider the diagnosis of a Spitz tumor to be supported. If not, genomic studies (CGH or FISH) could be considered as a further regard to prognosis and management.
Melanocytic Tumor of Uncertain Malignant Potential, Atypical Spitz Tumor Versus Spitzoid Melanoma

CLINICAL INFORMATION
Lesion of the arm in a 53-year-old woman, recently enlarged.

REASON FOR CONSULTATION
I am concerned about a Spitzoid melanoma.

DESCRIPTION
These sections show a moderately to highly cellular spindle cell proliferation, measuring 2 to 3 mm in diameter on the slide. It is comprised of large spindle, and/or epithelioid melanocytes, arranged singly and in nests with nests predominating, predominantly along the dermal–epidermal junction. There is a suggestion of clefting artifact with adjacent keratinocytes, and the epidermis is somewhat hyperplastic, without evidence of “consumption of the epidermis.” Globoid eosinophilic Kamino bodies are present at the interface. Similar cells protrude into the papillary dermis, expanding it, without infiltrating the reticular dermis. There is only slight evidence of maturation from superficial to deep; however, the cells even at the surface are relatively mature looking. The cells are strongly positive with Melan-A, and weakly positive with HMB 45, in a “top-heavy” staining pattern that reflects a form of maturation. There is one nest that is somewhat more expansile than the others, and comprised of somewhat larger cells, although measuring considerably less than 1 mm in maximum dimension. Importantly, mitotic figures are rare or absent with none seen in scanning multiple sections on the slide. Taking these findings together, I would agree that this is a Spitzoid lesion with atypical features, which I will interpret as follows:

FIGURE 7.1.4.1 A broad lesion, moderately to highly cellular, with an asymmetrical profile.
FIGURE 7.1.4.2 The lesion is well circumscribed at its periphery.

FIGURE 7.1.4.3 Kamino bodies are present at the interface (top left and center of this image).

FIGURE 7.1.4.4 and 7.1.4.5 The lesion is comprised of large epithelioid and/or spindle cells. There is only slight evidence of maturation to the base. However, the lesional cells are arranged in small clusters rather than forming a large expansile mass.

FIGURE 7.1.4.6 An HMB 45 stain demonstrates a “top-heavy” staining pattern.
COMMENT

I note that a p16 stain is pending and I would also recommend doing a Ki-67 study. As you know, homozygous loss of 9p21, which is the locus of p16, has been associated with aggressive behavior in a subset of Spitz tumors. If p16 is positive, then homozygous 9p21 loss cannot have occurred, which would be reassuring. Even in a worst-case scenario of interpreting this lesion as a Spitzoid melanoma, which I do not favor, it would be nonulcerated, and nonmitogenic, extending to Clark's level III, at a greatest Breslow thickness of less than 0.6 mm. This would therefore be a very low-risk lesion for which sentinel node staging would not be recommended. Although the lesion is completely excised, I would recommend consideration of an additional procedure to be sure it is completely removed, because changes extend within a fraction of a millimeter of the base and a peripheral margin of this biopsy specimen.

OVERALL COMMENT

Although this is a problematical lesion, especially in a patient of this age, its prognosis should be good even if it were interpreted as a melanoma, because of the absence of dermal mitotic activity. Many Spitzoid lesions, like this one, have “no mitoses at all,” which I consider to be a very reassuring finding even in the presence of cytologic atypia or failure of maturation. Since the publication of Gerami et al., identifying 9p21 loss as the major predictor of aggressive behavior in Spitzoid lesions, I also believe that a p16 stain can be very helpful (28). If p16 staining is absent in the tumor, then one can consider proceeding to genomic studies such as CGH or FISH.
7.1.5

Melanocytic Tumor of Uncertain Malignant Potential, Favor Atypical Spitz Tumor Versus Favor Spitzoid Melanoma

Clinical Information
Pigmented lesion of the right foot first digit in a 10-year-old child, thought to be of recent onset.

Reason for Consultation
Is the atypia in this lesion significant?

Description
These sections show a shave biopsy of skin containing a highly cellular proliferation of large spindle and/or epithelioid melanocytes, present in the epidermis as nests, some with clefting artifact, and single cells. The latter extend up into the epidermis in a quite prominent pagetoid scatter pattern across the lesion to the stratum corneum. Lesional cells extend into the papillary dermis where they show evidence of maturation along nevic lines. Dermal mitotic figures are rare or absent. HMB 45 staining is “top-heavy.” Ki-67 staining is minimal in the dermal component. p16 strongly stains lesional...
cells in the junctional and dermal components, with nuclear and cytoplasmic staining in a “checkerboard pattern,” which is quite characteristic of benign Spitzoid and other benign melanocytic proliferations. Taking these findings together, I would interpret this lesion as follows:

**FIGURE 7.1.5.3** Lesional cells extend into the epidermis and mature along nevic lines; however, they do not disperse into the reticular dermis at the base.

**FIGURE 7.1.5.4** The lesion is comprised of large spindle and/or epithelioid melanocytes that are quite uniform from side to side. There is quite striking pagetoid scatter of lesional cells into the epidermis. Kamino bodies are not readily visualized.

**FIGURE 7.1.5.5** Ki-67 stain demonstrates some proliferative activity of lesional cells in the epidermis, but little or none in the dermis.

**FIGURE 7.1.5.6** A p16 stain is strongly positive with nuclear and cytoplasmic reactivity, with a “checkerboard” pattern of the dermal component, where positive and negative cells alternate with one another, a pattern that is characteristically seen in dysplastic nevi and Spitz nevi/tumors.
The immunostains findings described above are all reassuring as is the absence of dermal mitoses. Pagetoid scatter is an atypical feature, but I would not regard this lesion as a melanoma. I would recommend consideration of an additional procedure to be sure this lesion has been completely removed with a clear margin of normal tissue, to allow for complete evaluation of it and also to preclude any possibility of persistence, recurrence, or possible future progression of it (MPATH DX category 2).

OVERALL COMMENT

Some examples of Spitzoid lesions in acral skin seem to combine features of Spitz tumors and special site nevi of acral skin. Pagetoid scatter, for example, seems to be quite common in these lesions, and should not be of great concern, especially in children. The interpretation of p16 staining is complicated by the fact that mature nevus cells do not express this marker. Immature nevus cells, such as those in dysplastic nevi and in Spitz nevi/tumors, typically express the p16 marker, and absence of expression in the atypical cells is a concerning feature for a possible aggressive lesion, although certainly not pathognomonic of malignancy.
Pagetoid Spitz Tumor Versus Superficial Spreading Melanoma

**Clinical Information**
Enclosed are slides and outside pathology report for the above referenced 10-year-old, shave excision of a lesion described by his mother as 3 mm red lesion on the right cheek, mandibular region.

**Reason for Consultation**
This lesion was evaluated at another regional medical center as malignant melanoma, superficial spreading type, Clark's level II, Breslow thickness 0.33 mm, with a mitotic rate of 1 per 10 high power fields. Melanocytic markers (Melan-A, HMB 45 and S 100) were described to delineate pagetoid spread into the overlying epidermis and invasion into the underlying superficial dermis. Proliferation markers (p53, Ki-67 and cyclin D1) are positive in the atypical component. These findings were considered to be consistent with the diagnosis of superficial spreading malignant melanoma. (See report.) Patient is being evaluated by our plastic surgeons and we are not sure that diagnostic criteria for malignant melanoma are present.

**Description**
These sections show a shave biopsy of a lesion that extends to both margins of a 2–3 mm specimen; however, by history, the lesion is only approximately 3 mm in diameter clinically. Therefore the sections are essentially representative of the entire lesion. If this were a biopsy of the much larger lesion, one might be more concerned. Even though the nature of the biopsy precludes evaluating the important criteria of circumscription and symmetry, this lesion presents with a fairly uniform population of spindle and/or epithelioid cells arranged singly and in nests along the dermal–epidermal junction.

*Figure 7.1.6.1* A shave biopsy of a broad, highly cellular lesion, transected at the specimen base. There is no evidence of ulceration or “consumption of the epidermis.”
There is pagetoid scatter of a few cells into the epidermis. The lesional cells have large nuclei with relatively regular nuclear membranes, pale chromatin, and small to medium nucleoli.

There is a moderate pagetoid proliferation of lesional cells into the epidermis, especially near the center of the lesion. Only a few cells protrude into the papillary dermis, where there is apparently some evidence of maturation; however, the cells are transected at the base. Therefore this important criterion is also not available for evaluation. An important feature is the presence of multiple globoid eosinophilic Kamino bodies at the interface, a feature highly characteristic of Spitz nevi. Mitotic activity and Ki-67 reactivity are low. The expression of p53 and cyclin D1 are not helpful diagnostically. In summary, I would interpret this material as follows:

Immunostaining for p16 is strongly positive.
Given the positive margins, I would recommend an additional procedure to be sure this lesion is completely removed and evaluate the remaining pathology (MPATH DX Category 2).

The presence of p16 staining rules out the possibility of chromosome 9p21 loss, which is the only chromosomal finding that has been convincingly associated with aggressive behavior in an evidence-based study (28). In addition, the diffuse nuclear and cytoplasmic staining and “checkerboard” staining patterns are those that are typically associated with benign nevi. Even if this lesion were interpreted as a melanoma, which I do not favor, its prognosis would be excellent based on the microstaging attributes mentioned above.
PSCN are benign melanocytic proliferations comprised of narrow elongated typically heavily pigmented spindle cells, predominantly located in the epidermis and also in the superficial papillary dermis. There is overlap between these lesions and Spitz nevi/tumors, especially those that are predominantly superficial as discussed in the previous section. We believe that there are sufficient differences to warrant maintaining this lesion as a separate category rather than terming it “pigmented Spitz nevus.” These lesions were first described by Richard Reed (1) and are also known as “Reed nevi.”

Several large series have described the clinical and histologic features of PSCN (1–7). Clinically, the lesions tend to be relatively small, ovoid or round symmetrical heavily pigmented often dark brown or black lesions. They are often noted to have recently appeared; however, they have usually become stable by the time of excision. A characteristic location is on the thigh of a young adult woman. However, they may be widely distributed, often being seen on the trunk, and in children and men as well as women.

Histologically, the lesions are characterized by a predominantly junctional proliferation of narrow elongated spindle cells that are arranged in fascicles that tend to be vertically oriented, a distinguishing feature compared to the horizontally oriented fascicles of dysplastic nevi. The nests tend to lack clefting artifact with adjacent keratinocytes, which is a distinguishing feature from classical Spitz nevi/tumors. The lesional cells typically contain abundant melanin pigment in relatively coarsely divided melanin pigment granules, which is another distinguishing feature from characteristic Spitz lesions. The lesional cell nuclei, like those in Spitz tumors, tend to be large, round or ovoid, with irregular nuclear membranes, and with pale chromatin and prominent nucleoli, although the latter tend to be somewhat less prominent in PSCN than in Spitz tumors. There may be single cells in addition to nests and there may be quite striking pagetoid scatter of single cells into the epidermis. Lesional cell mitoses are sometimes seen and are occasionally numerous in the junctional component. PSCN are often entirely junctional; however, when there is dermal involvement it is typically in the form of small nests of nevoid melanocytes that show evidence of maturation compared to the junctional component, losing pigment and becoming more grounded and smaller. It is relatively uncommon for spindle cells of these lesions to involve the reticular dermis, and when that is observed, concern for a spindle cell melanoma is raised.

Barnhill et al described the histopathologic features of 120 cases of pigmented spindle cell nevus from a consultative practice (6). The patients’ mean age was 25 years and females somewhat outnumbered males. Extremity lesions made up 70% of the total, with the thigh the most common site. The lesions were categorized into four variants based on architectural features and cytologic parameters. About 10% of the cases were designated typical PSCN and were characterized by fascicles of uniform pigmented
spindle cells without cytologic atypia and limited to the epidermis or papillary dermis. About 80% of the cases in this consultation practice were classified as atypical PSCN, based on architectural and/or cytologic atypia. Some of these had substantial numbers of epithelioid cells exhibiting overlap with Spitz nevus/tumor. Eight cases had overlap features with dysplastic nevus. Ten cases had fascicles of pigmented spindle cells involving the reticular dermis and were termed “plexiform” PSCN.

In terms of the etiologic/site/CSD classification of melanocytic tumors, PSCN are typically “no CSD” or “low CSD” lesions. This diagnosis should be made with great circumspection in the presence of moderate or severe CSD.

Limited clinical follow-up reported in the published series, as well as extensive anecdotal experience, has not identified aggressive behavior from PSCN, including the atypical variants. Nevertheless, knowledge of the varying presentations of this lesion is important for accurate diagnosis and distinction of these benign lesions from melanoma.

**MANAGEMENT OF PIGMENTED SPINDLE CELL NEVI**

These lesions are usually biopsied because of concern for the possibility of melanoma; however, their behavior is typically benign. It is generally believed that they should be completely excised, if only to allow for complete histologic evaluation (MPATH DX Category 2). Somewhat similar lesions that have a “thick” dermal component are beyond the scope of this treatise, but should be managed with greater circumspection, especially if there are dermal mitoses, when the differential diagnosis would include a spindle cell melanoma.

**References**

7.2.1

Pigmented Spindle Cell Nevus Versus Pagetoid Spitz Versus Superficial Spreading Melanoma

**Clinical Information**
A small darkly pigmented lesion of the left arm that recently developed in a 27-year-old woman.

**Reason for Consultation**
I favor a pigmented Spitz nevus but cannot rule out melanoma.

**Description**
These sections show a skin biopsy containing a relatively small, apparently well-circumscribed lesion that measures less than 2 mm in diameter on the slide, although it is present at one specimen border. It is comprised of a relatively uniform population of large spindle and/or epithelioid cells arranged as nests predominating, predominantly near the dermal–epidermal junction, with irregular epidermal hyperplasia rather than the more uniform rete ridge elongation that characterizes dysplastic nevi. Lesional cytology and architecture are quite suggestive of a Spitz or pigmented spindle cell lesion. A few small, ill-defined eosinophilic Kamino-like...
bodies are present at the interface. Lesional cells are quite uniform from side to side, and there is perhaps some limited evidence of maturation along nevic lines in the dermal component, which lacks any evidence of mitotic activity or tumorigenic proliferation. Although a few lesional cells are seen above the junction, there is no extensive pagetoid scatter into the epidermis and there is no extensive continuous proliferation between the rete. Taking these attributes together, I believe this lesion is best interpreted as a focally pagetoid Spitz/pigmented spindle cell nevus/tumor, which I would characterize as follows:

**FIGURE 7.2.1.3** With some exceptions, the nests lack clefting artifact with adjacent keratinocytes, a feature more often seen in Spitz tumors than in PSCN.

**FIGURE 7.2.1.4** A dermal component is confined to the papillary dermis as is more common in PSCN compared to Spitz tumors that generally involve the reticular dermis.

**FIGURE 7.2.1.5** A Melan-A stain demonstrates confluence of nests and pagetoid scatter of cells into the epidermis, features that could give rise to concern for superficial spreading melanoma. Lesional cells in the papillary dermis show evidence of maturation along nevic lines to a smaller cell type and dispersion as single cells.
**DIAGNOSIS**

Skin, left arm: Superficial spindle and epithelioid cell melanocytic proliferation, with features of Spitz and pigmented spindle cell nevus, present at a specimen margin, see Description and Comment.

**COMMENT**

Although the differential diagnosis could include a severely dysplastic nevus or, perhaps, an evolving or early established superficial Spitzoid melanoma, I strongly favor a diagnosis of Spitz/pigmented spindle cell neoplasm. These lesions are regarded as nevi in most instances, and malignant behavior is essentially anecdotal. In this present case, even if interpreted as a melanoma, the lesion would extend only to Clark's level II at a Breslow thickness of 0.30 mm. The dermal mitotic rate is zero, tumor-infiltrating lymphocytes are essentially absent, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. These are attributes of a lesion at minimal or zero risk of metastasis. Because of the differential diagnosis of severe dysplasia/melanoma in situ, the possibility of a lesion with some propensity for local persistence, recurrence, and possible future progression cannot entirely be ruled out, and because the lesion extends to specimen margins I would recommend an additional procedure to be sure it has been completely removed with, as minimum, a margin of normal skin around the scar of this procedure and any residual lesion (MPATH DX Category 2). Because of the differential diagnosis of severe dysplasia I would also recommend evaluation of this patient’s other melanoma risk factors, and especially if there is a family or personal history of melanoma, periodic surveillance of her skin may be appropriate.

**OVERALL COMMENT**

This case exemplifies the fact that there is overlap between the pigmented spindle cell nevus of Reed and the spindle and epithelioid cell nevus of Spitz. Nevertheless, there are differences between the two categories supporting the diagnostic distinction in most cases.
7.2.2

Atypical Pigmented Spindle Cell Nevus Versus Superficial Spreading Melanoma Versus Severely Dysplastic Nevus

**Clinical Information**

A darkly pigmented lesion of the thigh, of recent onset in a 59-year-old woman.

**Reason for Consultation**

I favor MIS arising in a severely atypical junctional nevus.

**Description**

These sections show a shave biopsy of skin, containing a moderately to highly cellular proliferation of spindle to epithelioid melanocytes, arranged singly and in nests generally predominating near the dermal–epidermal junction. The lesion is relatively symmetrical and is well circumscribed with the last cells on each side being in the form of small nests. Some nests bridge between adjacent elongated rete ridges. The lesional cells contain moderate to abundant melanin pigment in the form of relatively coarsely divided granules. A few small eosinophilic bodies are present along the interface.
There are also single cells, mainly near the dermal–epidermal junction.

The lesion is comprised predominantly of nests arranged near the tips and sides of elongated rete ridges. There is a patchy focally brisk lymphocytic infiltrate with melanophages in the dermis.

The lesional cells have uniformly large nuclei with regular nuclear membranes, pale chromatin, and small to medium nucleoli. These nuclear characteristics are typical of PSCN and Spitz nevi.
7.2.2

There are occasional mitotic figures in the junctional component (not shown). There is pagetoid scatter of single cells generally not beyond the lower third of the epidermis. In the center of the lesion, a few cells enter the papillary dermis, showing perhaps some slight evidence of maturation, and without tumorigenic proliferation or mitotic activity. These appearances present difficulties of interpretation between the possibilities of an atypical pigmented spindle cell nevus versus melanoma, in situ or minimally invasive, arising in a severely dysplastic nevus. I favor the former interpretation; however, in part because of the age of the patient, I would interpret this lesion descriptively as follows:

**DIAGNOSIS**

Skin, left posterior thigh: Superficial atypical melanocytic proliferation of uncertain significance, favor an atypical pigmented spindle cell nevus, see Description and Comment.

**COMMENT**

Although I favor a benign lesion, the possibility of a superficial nontumorigenic and nonmitogenic melanoma cannot be ruled out. If interpreted as a melanoma, this lesion would extend to Clark’s level II, at a greatest Breslow thickness of 0.25 mm. The dermal mitotic rate is zero, tumor-infiltrating lymphocytes sparse, there is no radial growth phase regression, there is no ulcer, there are no microscopic satellites, and there is no evidence of vascular, lymphatic, or neural invasion. This lesion would therefore be at minimal risk of metastasis. There is minimal to mild actinic elastosis in the adjacent skin, less than is typically seen in melanomas, even “low CSD” melanomas. The lesion appears to be completely excised with closest borders of about 1 mm. Nevertheless, because of this patient’s older age group, and the differential diagnosis, a reasonable approach to management might be to consider limited wide excision (MPATH DX Category 3 or 4).

**OVERALL COMMENT**

In the absence of “gold standard” definitive diagnostic tests, complete certainty is not always possible with regard to diagnosis, especially in these superficial melanocytic proliferations. While I favor a diagnosis of atypical pigmented spindle cell nevus, the possibility of a thin superficial spreading melanoma, or severely dysplastic nevus, cannot entirely be ruled out, especially in a patient in this older age group. FISH could potentially provide additional specificity of diagnosis; however, the findings are not likely to be definitive in individual cases. Conservative management appears appropriate in a case of this type. Because of the differential diagnosis of melanoma or dysplastic nevus, it would be judicious to evaluate this patient’s other risk factors for melanoma, and especially if she should have other clinically atypical nevi and/or family or personal history of melanoma, consideration of periodic surveillance could be appropriate.
Pigmented Spindle Cell Nevus Versus Severe Dysplasia or Evolving Melanoma In Situ

**Clinical Information**
A pigmented lesion on the back of a 6-year-old child of unknown duration.

**Reason for Consultation**
I would appreciate your opinion regarding this case.

**Figure 7.2.3.1** A broad, plaquelike moderately to highly cellular lesion with a somewhat asymmetrical profile, transected at one lateral specimen border.

**Figure 7.2.3.2** The lesion is well circumscribed at its periphery.

**Figure 7.2.3.3** The epidermis is somewhat irregularly thickened and thinned. There are nests as well as single cells near the dermal–epidermal junction.
7.2.3

**DESCRIPTION**

These sections show a punch biopsy of skin, submitted with no clinical history other than “lesion left back,” from a 6-year-old child, containing a moderately to highly cellular proliferation of nevoid to epithelioid melanocytes, with moderately abundant melanin pigment, and with a brisk bandlike lymphocytic infiltrate in the subjacent dermis. The lesional cell nuclei are relatively small and uniform, with small nucleoli. A few lesional cells appear to protrude into the papillary dermis, showing some evidence of maturation along nevic lines. In the dermis, also, there is a brisk bandlike lymphocytic infiltrate. The changes extend to one margin of the punch biopsy specimen. Not having the opportunity to review the entire lesion, I would therefore interpret this lesion descriptively as follows:

**FIGURE 7.2.3.4** The epidermis is somewhat irregularly thickened and thinned. There are nests as well as single cells near the dermal–epidermal junction. Most of the lesional cells are heavily pigmented. They tend to be vertically oriented narrow elongated spindle cells, although some have a more nevoid characteristic.

**FIGURE 7.2.3.5** There is some pagetoid scatter of lesional cells into the epidermis, although generally not beyond the lower third. The lesional cells have large nuclei with pale chromatin and regular nuclear membranes, and somewhat prominent nucleoli. There is a brisk bandlike lymphocytic infiltrate in the dermis.
CASE 3: PIGMENTED SPINDEL CELL NEVUS VERSUS SEVERE DYSPLASIA OR EVOLVING MELANOMA IN SITU

**7.2.3**

**DIAGNOSIS**

Skin, posterior back: Atypical intraepidermal and superficial dermal melanocytic proliferation, most consistent with a pigmented spindle cell nevus, with atypical features, see Description and Comment.

**COMMENT**

Assuming that this is a more or less complete representation of the entire lesion, I would consider the changes to be consistent with a pigmented spindle cell nevus. There are some unusual features, including a poorly nested junctional component and the bandlike infiltrate in the dermis, and if this is a biopsy of a much larger lesion, or if there were clinical concern about this present lesion because of a history of growth or change or clinically atypical morphology, I would recommend complete excision of it to rule out additional pathology, in case this could affect the diagnosis (MPATH DX category 2).

**OVERALL COMMENT**

In an older patient, a differential diagnosis of melanoma in situ of the superficial spreading type might be more tenable, and immunostaining for HMB 45, Ki-67, and p16 might be appropriate to provide for somewhat greater specificity. FISH could also be considered, if desired; however, whatever the diagnosis in this case, complete excision is certainly likely to be curative. Because there is a differential diagnosis with severe melanocytic dysplasia, it would be appropriate to consider this child’s family history and other risk factors, and if she should develop other clinically atypical nevi in the future, consideration of surveillance could be appropriate.
**CLINICAL INFORMATION**

A darkly pigmented lesion on the thigh of a 61-year-old woman, of recent onset.

**REASON FOR CONSULTATION**

We are concerned about melanoma versus an atypical nevus.

**DESCRIPTION**

These sections show a moderately cellular relatively small, well-circumscribed melanocytic proliferation that measures about 3 mm in diameter on the slide. It is comprised of relatively large nevoid to epithelioid and somewhat spindle cells, arranged predominantly in nests, predominantly near the dermal–epidermal junction. There are a few globoid eosinophilic bodies, consistent with small Kamino bodies at the interface. Cytologically, the lesional cells have abundant cytoplasm with relatively abundant, moderately to coarsely divided...
melanin pigment granules. The nuclei are small, generally regular, and the chromatin is homogeneous without prominent nucleoli. In the dermis, there are lymphocytes and melanophages, with only a few lesional cells, and certainly without any evidence of tumorigenic proliferation. There is also evidence of moderate actinic elastosis. In summary, I would interpret this material as follows:
7.2.4

**COMMENT**

Although not comprised of uniform, narrow elongated spindle cells, this lesion otherwise has the configuration of a pigmented spindle cell nevus of Reed. The presence of Kamino bodies supports this interpretation. Alternatively, the lesion could be considered as a junctional pigmented Spitz nevus. The history of relatively sudden appearance without continuing growth or change would also be supportive of this diagnosis. The differential diagnosis could include a dysplastic nevus with severe junctional melanocytic dysplasia. The possibility of superficial spreading melanoma in situ or even superficially invasive could also be considered. Changes extend close to a specimen border, and I would recommend an additional procedure to be sure this lesion has been completely removed, with a margin of normal tissue around the scar of this procedure and any residual lesion (MPATH DX Category 2). Because of the differential diagnosis of a dysplastic nevus, I would recommend evaluation of this patient’s other risk factors, and especially if she should have other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic surveillance may be appropriate. If these risk factors are absent, a diagnosis of a Spitz/pigmented spindle cell nevus would, to some extent, be supported.

**OVERALL COMMENT**

This lesion again illustrates overlap between PSCN, superficial pigmented Spitz nevi, dysplastic nevi, and superficial spreading melanoma. In the absence of dermal invasion, the prognosis for cure is, of course, excellent following complete excision. Because of the differential diagnosis of dysplastic nevus, and especially in this age group, the possibility that this lesion is a risk marker for future development of atypical pigmented lesions, including melanomas, should be considered.

**DIAGNOSIS**

Skin, right upper lateral thigh: Intraepidermal atypical melanocytic proliferation, of uncertain significance, with features of a pigmented Spitz/PSCN, present at specimen margins, see Description and Comment.
7.2.5

Superficial Atypical Melanocytic Proliferation of Uncertain Significance, Pigmented Spindle Cell Nevus Versus Spindle Cell Melanoma

**Clinical Information**
A variegated darkly pigmented lesion of recent onset, on the thigh of a 47-year-old woman.

**Reason for Consultation**
Our diagnosis is atypical compound nevus versus pigmented Spitz nevus versus melanoma.

**Description**
These sections show a shave excision specimen, containing a relatively small, moderately to highly cellular proliferation of spindle-shaped melanocytes in the epidermis, with a few cells descending into the papillary dermis. The lesion is reasonably well circumscribed and reasonably symmetrical. It is comprised predominantly of narrow elongated spindle cells, with variable but focally abundant coarsely divided melanin pigment granules in their cytoplasm. In addition, there is a tendency to pagetoid scatter of single cells into the epidermis across the lesion, focally reaching at least the stratum granulosum. The lesional cells that enter the dermis appear to show reasonable evidence of maturation along nevic lines, albeit to a somewhat limited extent.

**Figure 7.2.5.1** A relatively broad, moderately to highly cellular lesion with a somewhat asymmetrical architectural profile.
7.2.5

**FIGURES 7.2.5.2 and 7.2.5.3** The lesion is well circumscribed at its periphery with the last cells being arranged in a nest. There is moderate actinic elastosis in the dermis.

**FIGURE 7.2.5.4** The epidermal profile is somewhat irregularly thickened and nests are unevenly distributed, with some single cells in addition, mainly near the dermo-epidermal junction.

**FIGURE 7.2.5.5** Some lesional cells are heavily pigmented in the junctional component. Cells in the dermis are somewhat smaller and less pigmented and have somewhat enlarged nuclei with pale chromatin, regular nuclear membranes, and somewhat prominent nucleoli. There is no extensive high-level pagetoid scatter, no extensive continuous basal proliferation, and no severe uniform atypia.

Occasional small globoid ill-defined Kamino bodies are present in the junctional component. Although this lesion presents somewhat atypical features, I believe that it is a reasonable example of a pigmented spindle cell nevus, albeit with atypical features. It is presenting in a characteristic location; however, the presence of moderate actinic elastosis in the background skin is a somewhat concerning factor as is the (generally low-level) pagetoid scatter that is present across the lesion, and the relative failure of maturation of the dermal component. Pagetoid scatter of considerable degree
CASE 5: SUPERFICIAL ATYPICAL MELANOCYTIC PROLIFERATION OF UNCERTAIN SIGNIFICANCE

Although I favor the diagnosis of a pigmented spindle cell nevus of Reed, the differential diagnosis could include a severely dysplastic nevus or an evolving superficial melanoma. Even in the “worst-case scenario,” this lesion would be nonulcerated, nontumorigenic, and nonmitogenic, with a Breslow thickness of approximately 0.4 mm. This would be a lesion essentially without competence for metastasis. The lesion appears to be completely excised in the section planes available for study, with closest borders of approximately 2 mm laterally and 1 mm to the base of the specimen. Because of the differential diagnosis of a severely dysplastic nevus, I would recommend evaluation of this patient’s other melanoma risk factors, and especially if there should be other clinically atypical nevi and/or a family or personal history of melanoma, consideration of periodic skin surveillance may be appropriate.

As is often the case in these superficial lesions, even though there may be a differential diagnostic consideration of melanoma, it would be a lesion at almost vanishingly low risk for metastasis. In a current case, we would probably use Ki-67 and p16 staining as an adjunct to diagnosis, with a consideration of genomic studies if the findings from these immunostains were nonreassuring. If this lesion were not completely excised we would recommend an additional procedure to be sure it has been completely removed (MPATH DX Category 2).

**OVERALL COMMENT**

As is often the case in these superficial lesions, even though there may be a differential diagnostic consideration of melanoma, it would be a lesion at almost vanishingly low risk for metastasis. In a current case, we would probably use Ki-67 and p16 staining as an adjunct to diagnosis, with a consideration of genomic studies if the findings from these immunostains were nonreassuring. If this lesion were not completely excised we would recommend an additional procedure to be sure it has been completely removed (MPATH DX Category 2).
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