Less Common Variants of Cutaneous Melanoma

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ABSTRACT

Melanoma is among the most diverse neoplasms affecting man. Herein we will review the clinical and histologic features of some of the less common subtypes of cutaneous melanoma which clinicians and pathologists may encounter. There will be a disproportionate focus on the histopathology and prognosis, as the clinical presentation of these lesions is, in most cases, elusive and, in some cases, frankly deceptive. The discussion will include the following entities: desmoplastic melanoma, nevoid melanoma, spitzoid melanocytic neoplasms and spitz-like melanoma, angiotropic melanoma, blue nevus-like melanoma, and melanomas combined with basal or squamous cell carcinoma.

Keywords: melanoma, melanocytic nevus, Spitz tumor, blue nevus, angiotropism
INTRODUCTION

Cutaneous melanoma is one of the most heterogeneous and complex human neoplastic systems. Consequently, on a regular basis one encounters melanomas that are difficult to categorize as one of the four major subtypes.\(^1\) If there is difficulty in classifying an individual lesion as a “conventional” subtype of melanoma, there is clearly even greater difficulty in establishing whether less common variants of melanoma can be recognized based on objective evidence. In practical terms, the recognition and description of additional legitimate variants of melanoma must have some particular biological significance or relevance, and there must be objective criteria for their recognition and distinction from other presentations of melanoma. It is evident that this has not been achieved for many entities and much more basic research is needed.

The recognition and delineation of both conventional and less common variants of melanoma correspond to a wide range of clinical, microscopic, genetic, and molecular phenotypic characteristics. Clinical considerations for classification of melanoma subtype may include: 1) age of melanoma onset, e.g., birth, childhood and adolescence, and adulthood, 2) anatomic sites such as skin subject to continuous or intermittent sun exposure, acral and mucosal surfaces, 3) associations with precursor lesions such as congenital, dysplastic, or blue nevi, and 4) association with hereditary melanoma and atypical nevus kindreds.

A number of histological and cytological attributes have provided the basis for current melanoma classification: 1) intraepidermal arrangement (or growth pattern) of melanoma cells: lentiginous, pagetoid, nested, or absence of an intra-epidermal component, 2) epidermal surface configuration, e.g., verrucous, polypoid surface topography; 3) stromal alterations, e.g., desmoplasia, mucin deposition; 4) morphologic resemblance or mimicry of benign melanocytic neoplasms, i.e., “nevoid” melanoma, “spitzoid” melanoma, blue nevus-like melanoma (malignant blue nevus), resemblance to plexiform spindle cell nevus; 5) peculiar cytological characteristics, e.g., small cell, spindle cell, epithelioid cell, balloon cell, signet ring cell, rhabdoid cell, clear cell variants of melanoma, etc.; 6) other morphologic properties, e.g., neurotropism, neural differentiation, angiotropism, and adnexotropism; 7) pigmentary characteristics, e.g., amelanotic, pigment-synthesizing, or “animal-type” melanoma; and 8) host response and regression. Increasingly, molecular advances are providing new insights into the pathogenesis of melanoma. Thus, for example, particular mutations in the mitogen-activated protein (MAP) kinase, such as \(BRAF\), and the phosphatidylinositol 3 (PI3) signaling have suggested that there are different pathways for melanoma development.

This chapter will outline the clinical and histologic features of some of the less common variants or presentations of cutaneous melanoma which clinicians and pathologists are likely to encounter in clinical practice. There will be a disproportionate focus on the histopathology and prognosis, as the clinical presentation

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\(^1\)According to the current WHO classification, there are four major subtypes of melanoma: 1) Lentigo maligna melanoma, 2) Superficial spreading melanoma, 3) Acral lentiginous melanoma, and 4) Nodular melanoma. Although the latter classification has generally been accepted by many over the years, the artificiality and limitations of this classification have clearly been recognized. However, based on recent basic advances, it is increasingly evident that there are melanomas with different developmental origins owing to an interplay of intrinsic host factors such as molecular genotype and the environment, e.g., sun exposure. Thus, some refinements in the classification of melanoma are beginning to appear.
of these lesions is, in most cases, elusive and, in some cases, frankly deceptive when compared to conventional lesions of cutaneous melanoma. The discussion will include the following entities: desmoplastic melanoma, nevoid melanoma, spitzoid melanocytic neoplasms and spitz-like melanoma, angiotropic melanoma, blue nevus-like melanoma (malignant blue nevus), and melanomas combined with non-melanoma skin cancer.

■ DESMOPLASTIC MELANOMA AND DESMOPLASTIC NEUROTROPIC MELANOMA

Desmoplastic melanoma (DM) is a variant of spindle cell melanoma and is probably more appropriately termed a “desmoplastic melanocytic or neurocristic sarcoma” because of its phenotypic characteristics and biological behavior (1,3–14). As with “nevoid” melanoma (see below), DM harbors as perhaps its greatest significance, its accurate identification as cutaneous melanoma. The issue is compounded by the fact that the lesion is often amelanotic and highly infiltrative with a propensity for perineurial spread, which may contribute to its hallmark capacity for local recurrence—a feature that distinguishes it from other types of melanoma. Furthermore, DM often appears deceptively indolent initially with a very low frequency of regional lymph node metastases; however, particularly if not adequately excised and after local recurrence, often multiple, DM may become aggressive with a sarcomalike clinical course, sometimes with rather prototypic metastases to the lungs.

DM is among the most heterogenous variants of melanoma (4,6–14). With the characterization of larger numbers of DM, it has become increasing appreciated that DM constitutes a spectrum of melanomas, rather than a single entity. This spectrum encompasses: 1) pure DM which is typified by a pauci-cellular spindle cell nodule with desmoplastic stromal matrix; 2) desmoplastic-neurotropic melanoma (DNM), i.e., DM with associated neurotropism and/or neural differentiation; 3) pure neurotropic melanoma, i.e., a spindle cell melanoma with neurotropic phenotype and showing little or no desmplasia; 4) “mixed” or “combined” variants of DM/DNM which may exhibit an additional more cellular component of conventional melanoma, e.g., comprised of epithelioid and/or spindle cells (constituting about 10 to 50% or more of the DM) (12). The importance of recognizing the latter variants of DM is reflected in differences in biological behavior, prognosis, and management.

Clinical Features

The demographics of DM have been characterized by a predominance of males in the sixties and seventies, with the majority of reported lesions involving sun-damaged areas of the head and neck, although not at the exclusion of other body sites, including acral and mucosal surfaces (3–13). They present as nodules or plaques, sometimes depressed, which are very often amelanotic. However, in those cases that demonstrate pigmentation, it is often in the form of a conventional melanoma (often lentigo maligna) component, which happens to be congruent on a histologic level, as these lesions often represent the invasive component of melanomas involving chronically sun-exposed skin. (For purposes of this discussion, the conventional historical terms “lentigo maligna” and “lentigo maligna melanoma” are used to represent lentiginous in situ and invasive melanomas arising in chronically sun-damaged skin). However, desmoplastic melanoma can
also arise de novo, and it is this situation in which it poses the greatest diagnostic challenge. The lesion may also appear scar-like clinically, which is appropriate given the histologic profile. Rare variants of de novo DM appear to arise in melanocytic nevus remnants suggesting an additional pathway to DM.

Histopathologic Features

The histologic hallmark of DM is that of an ill-defined spindle cell neoplasm of varying concern with regard to density and cytologic atypia, that often demonstrates a highly infiltrative pattern of growth amidst sclerotic collagen fibers. In fact, the collagen density on scanning magnification resembles a scar, with the embedded cellularity being reminiscent of an accompanying fibroblastic component (Figure 1). Other variants of DM may demonstrate a more conspicuous spindle cell proliferation in which the degree of sclerosis is less ubiquitous throughout the lesion (Figure 2). The spindle cells may be present as single, markedly atypical, infiltrating cells (Fig. 3) or as a predominant arrangement of fascicles that sweep through dense collagen bundles in a manner reminiscent of a neural or smooth muscle proliferation. There is nuclear hyperchromasia and contour irregularity of the spindle cell forms (Figure 3), often with the added histologic features of lymphoid aggregates and solar elastosis. In fact, these latter two features in the setting of a sclerotic lesion, even with minimal or almost no cytologic atypia and inconspicuous mitotic activity, are often instrumental in arriving at the correct diagnosis. This is particularly important in those cases which are deceptively benign in appearance. The mitotic count in most tumors is relatively modest, adding to the diagnostic confusion. It is also of the utmost importance to always examine the dermal-epidermal junction in such cases for a subtle lentiginous melanocytic component possibly representative of an overlying atypical lentiginous melanocytic proliferation or melanoma in situ/lentigo maligna.

Neurotropic melanoma is often associated with atypical lentiginous melanocytic proliferation or lentiginous forms of melanoma. However, some NM may arise with any type of intraepidermal component, e.g., pagetoid involvement, or de novo without an intraepidermal component (13).

The term neurotropism refers to both the involvement of perineurium and endoneurium of cutaneous nerves by melanoma spindle cells and neural differentiation (Figure 4) (13). There may be considerable thickening of the perineurium and expansion of the endoneurial space by the tumor involvement. Extension of tumor along the cutaneous nerves may, however, be extensive and subtle. Histological clues to nerve involvement include the presence of hyperchromatic spindle cells in the perineurium or endoneurium and mucinous alteration of the nerve. Melanoma spindle cells involving cutaneous nerves usually show nuclear enlargement, hyperchromatism, and pleomorphism.

The term neurotropism also describes neural or Schwannian differentiation in a pattern resembling peripheral nerve sheath tumors such as neurofibromas or neuromas (“malignant neuroma”) and the recapitulation of perineurium and endoneurium. The tumor cells in such areas are characterized by serpiginous or wavy nuclear configurations and filamentous cytoplasmic processes. However, the tumor cells demonstrate loose fascicular arrangements, cytologic atypia, and occasional mitotic figures. Some tumors may
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**FIGURE 1**
Desmoplastic melanoma: scanning magnification discloses a large dermal fibrotic nodule.

**FIGURE 2**
Desmoplastic melanoma: fascicles of atypical spindle cells with stromal desmoplasia.

**FIGURE 3**
Desmoplastic melanoma: note the nuclear enlargement and pleomorphism of spindle cells.
be indistinguishable from a malignant peripheral nerve sheath tumor without observation of an atypical intraepidermal melanocytic proliferation.

Special Techniques

The immunohistochemical profile in most lesions of DM is characterized by S-100, Sox10, p75 neurotrophin receptor, and Vimentin positivity (4,9,10,14,15). Smooth muscle actin positivity indicative of myofibroblastic differentiation may be present in many cases. Melan A/Mart-1, HMB45, tyrosinase, and microphthalmia transcription factor (MITF) immunostains are almost always not expressed by the invasive spindle cell component. As a practical aside, it is important to exercise caution with regard to the S-100 stain in biopsy and re-excision specimens of DM, as there is almost invariably some degree of S-100 staining within the native dermis, and in the setting of non-melanocytic proliferations. These may be indicative of dermal antigen presenting cells. Such cells have also been documented in scars, where the nature of these cells have been postulated by different researchers as being representative of Langerhans cells (16), fibroblasts (17), and Schwann cells or regenerating nerve twigs (18). It is important to note that such cells do normally exist in the dermis as they represent a common pitfall that may contribute to an erroneous diagnosis of DM, particularly in the setting of scars that mimic DM, and also in the setting of re-excision specimens where they may be misinterpreted as being representative of residual DM.

The pathogenesis of DM remains unresolved. Some investigators, by way of immunohistochemical and ultrastructural analysis, have suggested that bidirectional differentiation is at play in these tumors (14). In one sense, DM and DNM, represent a spectrum of primitive neurocristic neoplasms with lines of differentiation including melanocytic with melanin synthesis, fibrocytic as evidenced by collagen and mucin production, myofibroblastic because of the expression of myogenic markers, and neurosustentacular, i.e., neurotropism and neural differentiation.

FIGURE 4
Neurotropic melanoma: pure invasive neurotropic component associated with lentigo maligna. Dermal invasive component is comprised of spindle cells arranged in fascicles resembling cutaneous nerves. There is little or no desmoplasia present. Higher magnification showing spindle cells with nuclear enlargement and pleomorphism.
Differential Diagnosis

The histologic differential diagnosis of DM includes: scar, desmoplastic or sclerosing nevus, desmoplastic Spitz tumor, sclerosing blue nevus, dermatofibroma, dermatofibrosarcoma protuberans (DFSP), peripheral nerve sheath tumors, sarcomas, spindle cell squamous cell carcinoma, and atypical fibroxanthoma. Perhaps the most important initial step in distinguishing a DM is an examination of the dermal-epidermal junction for the presence of a suspicious junctional melanocytic component and the lesion for the presence of melanin within tumor cells.

DM can quite incredibly mimic a scar. It is important to beware of “scars” that demonstrate (1) conspicuous cellularity, (2) solar elastosis, (3) lymphoid aggregates, (4) retained adnexal structures, and (5) a lack of horizontal fibrosis, vertically oriented vessels, and erythrocyte extravasation. Greater scrutiny should be applied to the cytomorphology in such cases, with regard to plump spindled cells with nuclear hyperchromasia and mitotic activity.

Desmoplastic/sclerosing nevi are usually well-circumscribed and show features of benign nevomelanocytes, only embedded in an inordinately sclerotic stroma. Aside from this sclerotic stroma, there is little resemblance in most instances, both architecturally and cytomorphologically, to DM.

Desmoplastic Spitz tumors often impart the appearance of a dermatofibroma, both clinically and histologically. Examination of the cytomorphology may raise some concern given the plumpness of the cells that is typical of spitzoid lesions. However, there is not a dominant spindled cytomorphology with wide dermal involvement. The lesions are usually relatively well-circumscribed and the cells are usually identifiable as being spitzoid. There is perhaps more chance for confusion with an atypical Spitz tumor rather than with a DM.

Sclerosing blue nevus, once again, resembles DM only by way of the dermal sclerosis. Dermal sclerosis is a relatively consistent feature of common blue nevi and sclerosing blue nevi. The presence of relatively bland epithelioid and fusiform cells with delicate to prominent cytoplasmic melanization dominates the histologic appearance.

Dermatofibromas, conventional and cellular, have been known to mimic DM, as some dermatofibromas indeed show a plump spindled cytomorphology with, in some cases, significant cytologic atypia and apparently increased mitotic activity. However, there is usually evidence of peripheral collagen trapping, no junctional melanocytic component, and, in most cases, a relatively bland cytology. In addition, the heterogeneity of the cellular populace, in the form of multinucleate and xanthomatized histiocytes, and a mixed inflammatory cell element, help to distinguish dermatofibroma from DM. This applies, even to those cases of cellular dermatofibroma and atypical fibrous histiocytoma which show dense dermal cellularity and bizarre cells. In the vast majority of cases, dermatofibroma variants can be distinguished from DM on routine staining.

DFSP demonstrates a highly cellular and diffuse dermal proliferation of spindled cells that involves the dermis and subcutis. The primary arrangement is storiform in most cases. Furthermore, the cytomorphology of DFSP is characteristically monotonous. In fact, it is more monotonous and homogeneous than dermatofibromas. The spindled nuclei are delicate and betray their malignant nature largely by way of architecture, rather than cytomorphology, in the form of diffuse involvement of
the dermis and subcutis with entrapment of subcutaneous adipocytes. Diagnostic confirmation is achieved via positive staining for CD34, and lesional negativity for S-100, allowing for histologic distinction from DM.

Neural proliferations such as malignant peripheral nerve sheath tumor (MPNST) pose a significant challenge, for in the absence of a junctional melanocytic component, there is histologic and immunohistochemical overlap with regard to S-100. However, a potentially useful discriminating feature in this setting is the patchy positivity of S-100 in MPNST as opposed to the diffuse lesional positivity for S-100 in most cases of DM. In addition, some MPNST’s may be associated with a background of neurofibroma. Further, MPNST arising in the skin is a distinctly uncommon phenomenon. However, distinguishing between these two conditions can pose a serious diagnostic challenge.

Sarcomas such as fibrosarcoma and leiomyosarcoma can show significant histologic overlap with DM. However, immunohistochemistry allows consistent differentiation from DM.

Spindle cell squamous cell carcinoma also shows considerable histologic overlap with DM. Scrutiny of the dermal-epidermal junction can be instrumental in such cases, should either keratinocyte atypia or a junctional melanocytic proliferation be identified. If this does not prove useful, immunohistochemistry is a reliable arbitrator in these cases.

Atypical fibroxanthoma can show spindle cell features. Once again, the immunohistochemical profile serves to resolve the diagnostic confusion.

The biological behavior of DM has been a subject of some controversy, largely due to the relatively low number of cases, and the increasing recognition of the fact that the natural history of this lesion appears to differ from that of conventional melanomas. Firstly, diagnostic delay, by virtue of the subtlety of the clinical and histologic findings, contributes significantly to the advanced Breslow depth that this lesion often demonstrates at diagnosis. Furthermore, even in those cases that are biopsied, limited lesional sampling may, in some cases, preclude the comprehensive histologic analysis that is required to diagnose these lesions. The mean Breslow depths, according to a large review of the literature, ranged from 2.0 to 6.5 mm (6). Most cases present with at least a Clark level IV. Also, local recurrence, more so than distant metastasis, distinguishes this tumor from other types of melanoma. Perineurial and endoneurial invasion in DNM and the ill-defined nature of these lesions, likely plays a significant role in this regard. It is held that distant spread is less common despite the advanced tumor thickness that is characteristic of DM (7). One study involving 129 patients and a mean tumor thickness of 4.2 mm reported recurrence in 39.5% of the cases, with 14% recurring locally. (8). A review of the literature, encompassing a total of 703 patients, documented a local tumor recurrence rate of 27.2%, a nodal metastatic rate of 7.1%, and a rate of systemic metastasis of 19.8% (6). A more recent study addressing the issue of nodal metastasis in DM reported one nodal metastasis in their cohort of 18 cases that underwent lymph node biopsy (7).

The prognosis of DM is generally regarded as being more favorable than that of conventional melanomas for a given tumor thickness. One study of 129 patients with a mean tumor thickness of 4.2 mm reported 76% and 64% respective 5 and 10-year rates of survival (12). In addition, a study performed at the Sydney Melanoma Unit in which they evaluated 280 patients with a mean tumor thickness of 2.5 mm
reported a 5-year survival of 75%. Ninety of these 280 patients represented cases of the neurotropic variety of desmoplastic melanoma. The researchers failed to demonstrate that perineural invasion affected rates of survival in DM. Further, they reported fewer lymph node metastases in DM as compared to those associated with conventional melanomas (9). It has further been reported that DM lesions greater than 4 mm in thickness demonstrate a 60% 5-year survival compared to 40% in non-desmoplastic melanomas (10). These findings contrast with those of a study involving 89 patients in which investigators reported rates of survival that were similar to those of non-desmoplastic melanoma of similar thickness (11). A more recent study engaged in a nuanced examination of the histologic features insofar as their prognostic contribution. They subdivided cases of DM into “pure” and “mixed” subtypes, being respectively representative of lesions with prominent stromal desmoplasia and those in which the desmoplastic component was simply an element of what was otherwise a more conventional melanoma. They reported that those patients classified as pure DM showed a significantly lower incidence of lymph node metastasis, and a lower 5-year melanoma-specific mortality as compared to the mixed DM patients. Further, they discovered that the melanoma-specific mortality was equal among the pure DM and conventional melanoma patients, despite a 3-fold higher median tumor depth in the former. Interestingly, they also reported that the lymph node metastases in the mixed DM patients were characterized by the non-desmoplastic component of the primary mixed DM lesions (12). It may, therefore, be reasonable, as Hawkins et al. suggest, to subclassify these lesions, and designate the pure forms of DM as Spindle Cell melanomas.

There exists, therefore, reasonable evidence to support the notion that DM's maintain a prognostic advantage when compared to conventional lesions of cutaneous melanoma. However, the question that is perhaps more intriguing relates to the pathobiology of this neoplasm. Specifically, should a lesion that deviates, on a morphologic, immunohistochemical, and behavioral basis, from melanoma, continued to be classified as a melanoma versus a “primitive melanocytic or neurocristic spindle cell sarcoma” (one can recall the use of the historical term “melanosarcoma”)? Perhaps future studies will seek to address this issue.

Management

DM carries a high risk for local recurrence which is directly related to its frequent amelanotic appearance, often advanced stage at the time of diagnosis, Breslow thickness > 4.0 mm, and neurotropic and angiotropic properties, as mentioned above. Thus, resection of DM with clear surgical margins as early as possible in its development is crucial to its successful clinical management. Although not systematically studied, most surgeons recommend a minimum clearance of at least 1 to 3 cm. As already discussed, there is increasing evidence that SLNB may not be indicated for “pure” variants of DM because of their low incidence of regional lymph node metastases

NEVOID MELANOMA

It is well established that melanoma may show differentiation along the lines of almost every variant of benign melanocytic nevus or tumor. Thus, a priori a subset of melanomas closely resembles melanocytic nevi. Hence the rubric
“nevoid” melanoma has appeared in the literature as a direct result of this fundamental diagnostic problem of differentiating melanoma from nevus. In this article “nevoid” melanoma (NM) is defined as a tentative group of melanomas that more or less recapitulate the architectural configuration and cytomorphology of melanocytic nevi, yet concomitantly demonstrate histologic criteria for, and the biological behavior of, melanoma (1,13,19–24). However one can make the case that until a series of “NMs” have been characterized at the clinical, histologic and molecular levels with long-term follow-up, there is no scientific basis that NMs exist as a legitimate entity. Since many such lesions are not diagnosed initially and are detected only in retrospect, the histologic diagnosis of NM remains controversial and consensus criteria have not been established. Suffice to say that nevoid melanoma remains a subject of ongoing research. In any case, this problem of the distinction of melanoma from nevus is among the most treacherous diagnostic problems in all of dermatopathology, and as such, carries significant medicolegal implications.

Clinical Features

Although more rigorous studies are needed, from the NMs reported thus far in the literature, they seem generally comparable to conventional melanomas in terms of demographic characteristics. Most cases have been reported in women, with some degree of predilection for the legs and trunk (1, 13, 19, 20). This condition has no clinically distinctive features. In fact, it most often imparts the appearance of a nevus, which stands to reason when one understands the nature of the histopathology.

Histopathologic Features

The histologic diagnosis of “nevoid” melanoma is notoriously difficult since important standard criteria for melanoma are usually absent. For example, many such lesions are often less than 5 to 7 mm in greatest diameter; asymmetry, poor circumscription, and pagetoid melanocytosis are absent or minimal; apparent “maturation” may be present; and the constituent melanocytes may be smaller and less atypical than the usual high-grade melanoma cells (1, 13,19–24). Thus scanning magnification, in most cases, reveals a relatively small-diameter, predominately or purely dermal nevomelanocytic proliferation that shows symmetry and sharp circumscription with even an element of maturation by virtue of the diminution of the cellular density with lesional descent (Figs. 5–7). The extent to which the overall size and configuration of the individual lesion resembles or deviates from that of a nevus compromises or reinforces the histopathologist’s suspicion for melanoma. Some cases may be verrucous or polypoid in configuration and, importantly, some proportion of cases are amelanotic.

The common denominators among many nevoid melanomas that should alert the pathologist to the diagnosis include: 1) dermal mitoses, 2) a sheet-like appearance, i.e., hypercellularity and crowding of dermal melanocytes, 3) a monomorphous appearance of melanocytes, 4) subtle but definite cytologic atypia as evidenced by nuclear enlargement, nuclear pleomorphism, irregularity of nuclear membranes, coarsening of nuclear chromatin, and often distinct nucleoli (Figure 8), 5) the lack of conventional maturation and presence of irregular infiltrating features at the base, and 6) angiotropism. Perhaps the minimal essential criteria needed for (nevoid) melanoma are dermal mitoses, a
FIGURE 5
Nevoid melanoma: scanning magnification demonstrating a symmetrical and well-circumscribed dermal melanocytic proliferation.

FIGURE 6
Nevoid melanoma: note diminished cellular size and density with lesional descent suggesting maturation. There are discreet dermal nests of melanocytes suggesting a nevus.

FIGURE 7
Nevoid melanoma: note cords of melanocytes with infiltrative pattern in deeper dermis.
sheet-like pattern, and cytologic atypia. It is clear that the greater the number of criteria present the greater the certitude of the diagnosis of melanoma. In terms of cytology, the melanocytes vary from relatively small cuboidal cells to enlarged round, ovoid or spindled cells. Typically, melanoma cells of the same size are present throughout the lesion and at the base, albeit with, in some cases, the added element of decreased cellular density suggesting maturation. In some instances, cellular and nuclear sizes of melanocytes are slightly diminished with depth. This is accompanied by increased mitotic activity in most lesions. Mitotic activity is particularly contributory to the diagnosis when it involves the lower third of the dermal melanocytic populace. The intraepidermal component, if present, may be subtle or limited in nature. One may observe melanocytes arranged as single cells and/or in junctional nests along the dermal-epidermal junction. The nesting may result in confluence of nested aggregates of melanocytes replacing the basilar portion of the epidermis. The epidermis is frequently effaced, thinned, and associated with dermal-epidermal separation. Pagetoid spread may be present in a proportion of cases and is an important finding in confirming a diagnosis of melanoma; however it is often not a conspicuous feature. Inflammation and necrosis are less conspicuous than in conventional melanomas, or may be altogether absent. In some proportion of cases, the proliferation can assume a perineural and angiotropic pattern of spread.

Differential Diagnosis
The differential diagnosis of NM includes: 1) various types of melanocytic nevi with atypical features, and 2) metastatic melanoma. The difficulty with this diagnosis, as already mentioned, is directly related to the distinction of melanoma from nevus and that any individual melanocytic lesion may show a spectrum of features shared by both melanoma and nevi. As in all things, a comprehensive analysis and a high index of suspicion and sensitivity to certain subtle clues often leads one to the correct diagnosis. A melanocytic lesion may raise definite diagnostic suspicion for melanoma on an almost visceral level at scanning magnification. Such suspect lesions often impart a sheet-like or crowded configuration and
monomorphous appearance of the dermal component. In addition, the lesional base is usually ill-defined with hyperchromatic cells infiltrating the dermis in a single-cell and cord-like fashion. Higher magnification often reveals round, ovoid or spindled melanocytes resembling nevus cells but also showing some cellular enlargement, nuclear enlargement, irregularity of nuclear contours, thickening of nuclear membranes, and commonly subtle but distinct nucleoli. Further examination reveals the presence of variable mitotic activity, sometimes limited in number. Mitoses located in the lower third of the lesion, in this setting, provide additional support for melanoma.

Certain variants of melanocytic nevi that are especially difficult to distinguish from (“nevoid”) melanomas include polypoid cellular compound or dermal nevi, congenital and congenital-pattern nevi, melanocytic nevi with halo reactions, traumatized and inflamed nevi, acquired and congenital melanocytic nevi with atypical dermal nodule formation, melanocytic nevi removed from pregnant women, and melanocytic nevi from particular anatomic sites such as the vulva, breast, or scalp. The characteristics suggesting melanoma are the very same that have been emphasized above: dermal mitoses, the appearance of dermal hypercellularity, a monomorphous quality of dermal melanocytes, cytologic atypia, and perhaps diminished maturation. As with all melanocytic lesions one must have certain essential clinical information including age, gender, anatomic site, and history of melanoma, pregnancy, trauma or other pertinent factors before definitively interpreting melanocytic lesions. Likewise, the histopathologist must have at least the essential histologic criteria present and, optimally, additional abnormal features to assure a confident diagnosis of melanoma. Thus, in general the diagnosis of melanoma cannot be based on a single abnormal finding. For example, mitotic figures can be seen in nevi, especially in certain contexts such as nevi in young individuals, polypoid cellular nevi, nevi with halo reactions, and atypical dermal nodules associated with nevi, and traumatized nevi. Often such mitoses are noted only in the superficial half of such nevi and the mitotic rates are usually about 1 to 4 per mm². The mere presence of such mitotic activity, in and of itself, does not and should not prompt a more serious diagnosis. However more significant mitotic rates, mitoses observed at the base of a lesion, and atypical forms should prompt careful scrutiny for other features supporting melanoma. Hypercellularity also occurs in nevi with some frequency; however such hypercellular nevi usually display diminished cellularity and maturation with depth. Cytologic “atypia”, depending upon one’s threshold, is seen in most nevi in the form of senescent atypia, characterized by nuclear enlargement with some contour irregularity and multinucleation. However, the degree of consistent nuclear enlargement, nuclear irregularity, thickening of nuclear membranes, and distinctively enlarged and multiple nucleoli observed in melanoma are usually lacking in nevi. Maturation is a variable phenomenon in ordinary nevi, depending upon the depth of dermal extension, involvement of adnexal structures, and the like.

Some advocate the employment of Ki-67 and HMB45 as adjunctive diagnostic measures; however, in the authors’ opinion, such ancillary studies are limited in their diagnostic utility.

It is important to note that the spectrum of NM is clearly on a continuum with conventional “nodular” melanoma and the distinction of the two is probably artificial and not reproducible in many cases. It should be emphasized that as with
nodular melanoma one should always consider metastatic melanoma in the differential diagnosis of “nevoid” melanomas. Although criteria have been suggested for distinguishing metastatic from primary melanoma, often clinical information is crucial to establishing a lesion as primary vs. metastatic.

The outcome from reviewing many such lesions raising suspicion for nevoid melanoma results in the major groupings of 1) controversial lesions including many atypical nevi that lack unequivocal criteria for melanoma and 2) lesions interpreted as nevoid melanoma by a consensus of observers or based on an adverse event such as metastasis. Thus, one will encounter lesions lacking sufficient criteria for melanoma. Such lesions should be reported descriptively as atypical melanocytic neoplasms and possibly as biologically indeterminate for some tumors, with the additional qualification that a melanoma cannot be entirely excluded. Further, if the lesion approaches one millimeter in depth, the dilemma is further compounded with regard to the inclusionary criteria for sentinel lymph node biopsy. There is as yet no viable solution to this dilemma. However, the most sound approach is likely an honest discussion of the situation with the patient, and possibly the surgical oncologist, with a presentation of all facts in hopes of arriving at a mutually agreeable course of action.

The prognosis of nevoid melanomas, if established as melanoma, appears indistinguishable from that of conventional melanomas in the studies thus far published. Thus, the standard prognostic factors including clinical stage and Breslow thickness are the major determinates of clinical outcome. However, the prognosis of such lesions in general requires more rigorous study.

Management

Patients with melanocytic lesions established as nevoid melanoma should be managed as conventional melanomas.

SPITZOID MELANOCYTIC NEOPLASMS AND SPITZ-LIKE MELANOMA

Spitzoid melanocytic neoplasms have occupied a special niche in the melanocytic neoplastic system for many years, and there is increasing evidence that they are a biologically unique melanocytic neoplasm (13, 25–53). Yet there are still many unresolved questions with respect to the biological nature, natural history, and biological potential of spitzoid melanocytic lesions in general (32–35). For example, do malignant spitzoid lesions exist as such; do they exist in particular age groups such as prepubertal children or even in older individuals; do they have a unique molecular genotype; do they have a different biological potential, possibly less aggressive, than conventional melanomas? Are Spitz tumors in general (or a subset of Spitz tumors) capable of spreading or metastasizing beyond the primary site yet not constitute a conventional malignant neoplasm and metastasis?

As with “nevoid” melanoma the term “spitzoid” melanoma has surfaced in the medical literature as a direct result of the difficulty or impossibility in some cases of distinguishing melanoma from Spitz tumors. One particular source for the use of the term “spitzoid” melanoma (SM) has come about from the retrospective diagnoses of melanocytic lesions (as cutaneous melanoma) which had been initially interpreted as “Spitz nevus” and have subsequently shown clearly documented adverse events such as lymph node metastases,
more distant metastases, and/or death. Thus, although the term SM would seem to have merit, in fact “SM” has been used with such imprecision in the literature that the term itself has become almost meaningless in the authors’ view (32,53). The essential problem is the indiscriminate application of this term to a heterogeneous group of spitzoid-appearing lesions that differ considerably in terms of many phenotypic and genotypic characteristics and biological potential (Figure 9) (32–35, 39–53). For example, the term has been applied to:

(1) lesions originally interpreted as Spitz nevi and following an adverse event are in retrospect diagnosed as melanoma;
(2) conventional (or “typical”), atypical or controversial spitzoid tumors in children, adolescents, and adults with or without clinical lymph node metastases and no apparent progression of disease;
(3) atypical or controversial spitzoid tumors in children and adolescents or adults with clinical lymph node metastases, no apparent progression of disease, and with or without genotypic aberrations;
(4) atypical or controversial spitzoid tumors in children and adolescents and adults with positive sentinel lymph node involvement and no apparent disease progression (54–57);
(5) atypical or controversial spitzoid tumors with chromosomal aberrations associated with conventional melanoma;
(6) conventional melanomas having some resemblance to Spitz tumors.

For the time being, the authors recommend that the use of the term “spitzoid” melanoma should be curtailed until rigorous guidelines regarding its usage are formulated.

Spitzoid lesions, like other melanocytic lesions, occur along a histologic continuum of benign, atypical, and malignant, perhaps low-grade and high-grade, and must be evaluated utilizing all clinical, histopathologic, and other criteria available (32,33, 36–38, 41–51). After examination, one can usually assign a given lesion to one of three categories:

(1) Spitz tumors without appreciable disease, and with or without genotypic aberrations;
(2) conventional (or “typical”), atypical or controversial spitzoid tumors in children, adolescents, and adults with or without clinical lymph node metastases and no apparent progression of disease;
(3) atypical or controversial spitzoid tumors in children and adolescents or adults with clinical lymph node metastases, no apparent progression of disease, and with or without genotypic aberrations;
(4) atypical or controversial spitzoid tumors in children and adolescents and adults with positive sentinel lymph node involvement and no apparent disease progression (54–57);
(5) atypical or controversial spitzoid tumors with chromosomal aberrations associated with conventional melanoma;
(6) conventional melanomas having some resemblance to Spitz tumors.

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abnormality, (2) Spitz tumors with one or more atypical features (atypical Spitz tumor) including those with indeterminate biological or malignant potential, possibly including a percentage of low-grade malignant lesions, and (3) cutaneous melanoma, potentially low-grade and high-grade (32).

The authors believe that it is overly simplistic to impose an (often arbitrary) interpretation of either ‘Spitz’s nevus’ or melanoma on every spitzoid lesion (32). This approach is not satisfactory for patient care and does not provide a realistic methodology for dealing prospectively with such a difficult problem. Such an exercise undoubtedly results in both the overdiagnosis of melanoma and underrecognition of atypical or ambiguous lesions requiring more medical attention. Patients may unfairly suffer the psychological burden of a grave diagnosis and be subjected to overly aggressive and potentially harmful therapies. Conversely, some proportion of patients will have the false and unjustified assurances of a benign diagnosis and may not receive appropriate treatment and follow-up.

Clinical Features

The majority of Spitz tumors occur in young individuals particularly under the age of 10–20 years (25–32). The older the patient, especially individuals beyond the age of 40 years, the greater the likelihood of malignancy. However, Spitz tumors may occur with greater frequency in older adults than has been appreciated owing to the propensity of many pathologists to a priori interpret them as melanoma.

Other clinical factors such as the location of the tumor, clinical appearance, history of recent changes in a long-standing stable lesion, and family history of melanoma should be considered carefully. Spitz tumors commonly involve the extremities and face. The location of atypical tumors on sites less commonly involved by Spitz tumor, such as the back, is also another factor suggesting careful scrutiny of the lesion for melanoma.

In general, Spitz tumors are relatively small (often < 5 to 6 mm in diameter), symmetrical, and well-defined, dome-shaped nodules or plaques with uniform pink or reddish coloration. Roughly 10% are pigmented. Atypical variants show larger diameters (i.e., > 5 mm), particularly greater than 1 cm and increasingly abnormal gross morphologic features including irregular borders, irregular topography, ulceration, and irregular coloration.

Histopathologic Features

The histological interpretation of spitzoid melanocytic neoplasms, as with all melanocytic lesions, first of all involves a qualitative (or gestalt) assessment as to whether the lesion of interest is obvious melanoma or not. Even if considered unequivocal conventional melanoma, the histopathologist should be able to systematically analyze the lesion with a battery of fairly standardized histological criteria and other techniques in order to objectively corroborate his/her interpretation of melanoma, or, alternatively, a spitzoid melanocytic neoplasm with or without atypical properties (see Figs. 10–16) (32,33 52,53). These principal microscopic attributes include the following:

Size (diameter in mm): Most typical Spitz nevi/tumors measure less than 5–6 mm. Size beyond 5 to 6 mm, especially > 10 mm is generally considered abnormal. This is a continuous variable and there are obvious exceptions to this criterion.
FIGURE 10
Compound Spitz tumor: scanning magnification demonstrates a prototypic conventional Spitz tumor. This lesion is characterized by small-diameter, sharp circumscription, symmetry, and absence of the following: ulceration, effacement of the epidermis, dermal mitoses, and extension into subcutaneous fat.

FIGURE 11
Atypical compound spitzoid melanocytic neoplasm: biopsy sampling of lesion from the foot of a 17-year-old female demonstrating a compound melanocytic neoplasm with asymmetry of the junctional and dermal components and lack of maturation. Note nodular portion of the lesion in the deep dermis. FISH testing revealed loss of 6q23.

FIGURE 12
Atypical compound spitzoid melanocytic neoplasm: higher magnification of deep dermal nodule.
**FIGURE 13**
Atypical compound spitzoid melanocytic neoplasm: higher magnification of deep dermal nodule. Note large atypical epithelioid melanocytes with conspicuous nucleoli and mitotic figures. The mitotic rate was 3 per mm$^2$.

**FIGURE 14**
Melanoma resembling a Spitz tumor: scanning magnification shows a poorly circumscribed, asymmetric and ulcerated atypical melanocytic proliferation measuring 8 mm in diameter and 6.1 mm in thickness.

**FIGURE 15**
Melanoma resembling a Spitz tumor: higher magnification of dermal component demonstrating high cellular density and confluence of melanocytes. The mitotic rate was 7 per mm$^2$. 
Tumor thickness (measured in mm): Significant (Breslow) depth and involvement of the subcutaneous fat are considered abnormal.

Asymmetry: Increasing asymmetry is abnormal as in all melanocytic lesions.

Epidermal configuration: Most typical Spitz nevi/tumors show a prototypic symmetrical and crescent-shaped or plaque-type pattern of epidermal hyperplasia without effacement or disruption of the epidermis by the spitzoid melanocytic elements. In fact, the relationship between junctional nests and fascicles of melanocytes and the epidermis is unique: the nests and especially the fascicles of melanocytes insinuate between keratinocytes in a serpiginous and nondisruptive fashion quite unlike the consumptive and obliteratorive effects of melanoma. Even with pagetoid melanocytosis and transepidermal elimination of nests of melanocytes the epidermis generally remains rather surprisingly undisturbed. Another characteristic feature is the clefting between the epidermis and the superficial aspects of junctional nests of melanocytes (Figs. 22, 23). Unfortunately, many spitzoid lesions are traumatized and consequently they do not often maintain the orderly and symmetrical properties described above to the degree ideally one may expect.

Ulceration: Ulceration is an abnormal finding; however, ulceration is often at least partially induced by trauma and its significance may vary.

Poor circumscription: The most banal Spitz nevi/tumors tend to be sharply circumscribed at their peripheries whereas atypical lesions are often less well-circumscribed. This parameter obviously correlates with asymmetry and other organizational attributes.

Pagetoid melanocytosis: Pagetoid spread may be observed not infrequently in Spitz tumors. However, such pagetoid spread should be limited to the lower half of epidermis, should not extend peripherally, should be only focal, and sparsely cellular. More extensive pagetoid spread involving the upper half of the epidermis, a large segment of the lesion (one or more high-power fields), and in a single-cell or small nested pattern is distinctly abnormal. External trauma may be a factor leading to excessive pagetoid spread in benign lesions.
Prominent confluence and high cellular density of melanocytes: These two parameters are closely correlated and are among the most important criteria for assessing melanocytic lesions. Unfortunately, these characteristics are subjective and therefore difficult to recognize reliably and reproducibly. These two parameters are also often closely linked to diminished or absent maturation (see below). Confluent cellular aggregates or nodules of considerable size and with crowded appearance in the dermal component, particularly replacing the dermis, and extending deep without maturation are also decidedly atypical. Breslow thickness obviously may capture the significance of such expansile dermal nodules. One caveat is the occurrence of such nodules in Spitz tumors of young children, which may take on less importance in the latter context.

Lack of zonation and maturation: Zonation refers to the side-to-side homogeneity often observed in typical Spitz tumors. Whereas maturation is the progressively diminished sizes of nests of melanocytes and gradual dispersion of melanocytes to smaller nests and single cells with depth. The latter phenomenon, in its most developed state, involves a nondisruptive infiltration of melanocytes among collagen bundles and involution of melanocytes to smaller cells with smaller nuclei with depth. Therefore, the nonuniformity (heterogeneity of organization) of a lesion when scanned from side to side and the continued presence of nests and fascicles of similar sizes deep indicate potentially aggressive properties.

Few or no dull pink (Kamino) bodies: Although this feature may be seen in both Spitz tumors and melanomas, the presence of clear cut aggregates of Kamino bodies may be a marker suggesting a more typical Spitz tumor.

Mitotic rate per mm²: The mitotic rate of the dermal component is one of the most important parameters for evaluating spitzoid lesions as increasing proliferative rate seems to correlate with likelihood of aggressive behavior or malignancy. Furthermore, this parameter is quantifiable. Mitoses observed in the deepest parts of the dermal or subcutaneous component—that is, near the deep margin, also seem to have greater significance than more superficially located mitoses. There are clearly no absolute thresholds for the mitotic rate being indicative of benignancy or malignancy, and the authors caution against using mitotic rate alone (or any single criterion alone) for the interpretation of a melanocytic lesion. It is important in almost all instances to have several distinctly abnormal parameters present to confirm malignancy. Every lesion must be systematically assessed on a case-by-case basis. In any event, high mitotic rates, particularly beyond six mitoses per mm² raise concern for malignancy. Unusual circumstances that may confound the importance of high mitotic rate include: (1) developing Spitz tumors may be in a growth phase and mitotic rate may have less significance, (2) Spitz tumors in very young individuals may have somewhat higher mitotic rates, and (3) external trauma and significant inflammation may be factors leading to higher mitotic rates.

Cytologic attributes suggesting a more atypical spitzoid lesion and possibly melanoma include heterogeneity of cell type throughout the lesion, particularly in an asymmetrical or haphazard pattern; high-nuclear-to-cytoplasmic ratios; granular or ‘dusty’ cytoplasm vs the ground glass cytoplasm of Spitz melanocytes; absence of delicate or dispersed chromatin patterns with thickening of nuclear membranes; a large proportion of melanocytes with hyperchromatic nuclei; and the presence of large eosinophilic nucleoli.
Ancillary Techniques

Immunohistochemistry

Spitzoid lesions have been evaluated with a variety of bio-markers. S-100 protein and Melan-A/Mart-1 show diffuse expression throughout both Spitz tumors and melanoma in contrast to the characteristic diminished expression of HMB45, tyrosinase, and other markers toward the base of Spitz tumors. In addition, there is a gradient of diminished proliferation with increasing depth of the dermal component paralleling mitotic rate and cyclin D1 expression in Spitz tumors. Although requiring much more study for standardization, Ki-67 expression may be useful in the risk stratification of Spitz tumors (33, 36–38, 48). For example, in one study atypical Spitz tumors had a mean Ki-67 labeling index of 10% relative to 0.53% in ordinary nevi, 5.04% in conventional Spitz tumors, and 36.83% in conventional melanomas (37); whereas in another study a Ki-67 proliferation index less than 2% favored a conventional Spitz tumor, one greater than 10% melanoma, and indices between 2 and 10% were equivocal (36). The qualitative loss of Ki-67 expression vs continued labeling with depth as with other markers such as HMB-45 also correlates with maturation and a less atypical lesion.

Spitz tumors also appear to exhibit lower rates of p53, bcl-2, and fatty acid synthase expression compared to melanoma (37, 38). The loss of p16 expression in atypical spitzoid melanocytic neoplasms also may favor melanoma (48). Although many of the latter markers are of interest, they require rigorous assessment with greater numbers of cases and long term follow-up in order determine whether they have any predictive value in the evaluation of spitzoid lesions.

Comparative Genomic Hybridization and Fluorescence In Situ Hybridization

From the small number of studies thus far published, it seems that a relatively large proportion of Spitz tumors including a significant percentage of atypical or controversial variants fail to show chromosomal or genetic aberrations by comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) (39–47). That is to say, in general, the lesions studied do not show chromosomal aberrations, as are usually observed in conventional melanomas. In an early study of Spitz tumors, about 15% of the lesions demonstrated an increased copy number of chromosome 11p, generally correlating with Spitz tumors which were often larger in size, dermal-based, desmoplastic, with vesicular nuclei in melanocytes, dermal infiltrating features, and were associated with HRAS mutation; whereas 85% showed no chromosomal aberrations (39, 40). A recent small series of spitzoid melanocytic neoplasms analyzed by array CGH has shown that among 16 atypical Spitz tumors, 44% showed chromosomal aberrations, whereas 56% showed none (41). The chromosomal aberrations documented in these 7 ASTs were unusual and not observed to date in conventional melanomas. Another recent investigation of 75 atypical Spitz tumors utilizing six FISH probes targeting major melanoma chromosomal loci, has suggested that gains in 6p25 and 11q13 and homozygous deletion of 9p21 may correlate with increased risk for aggressive behavior and potentially death, respectively (45, 46). However, another comprehensive analysis of FISH results has shown almost comparable rates of FISH positivity in “atypical Spitz tumors” (62% FISH positive) and “Spitzoid melanomas” (71% FISH positive) (47). From this information spitzoid melanocytic lesions may be categorized as: 1) spitzoid...
melanocytic lesions without any apparent genotypic aberrations, perhaps corresponding to conventional or typical Spitz tumors; 2) spitzoid lesions with various genotypic aberrations, some newly-described and not associated with conventional melanoma, and not having clearly established biological significance, perhaps corresponding to atypical Spitz tumors including possibly some low-grade neoplasms; and 3) spitzoid lesions with genotypic aberrations usually associated with conventional melanoma, perhaps corresponding to both low-grade spitzoid melanocytic neoplasms and some high-grade neoplasms (probably including conventional melanoma). The latter scheme is not new but may potentially have greater predictive value for disease progression and outcome but still requires rigorous validation (32–34, 47).

Therefore, it is certain that there must be much more detailed and objective clinical, histologic, and molecular characterization of spitzoid melanocytic lesions, correlation with natural history, particularly with rare cases manifesting distant metastases and death, and long-term follow-up, perhaps of at least 15 years, in order to clearly define distinct patient subgroups (32, 34, 47, 53).

Loss of Heterozygosity
Two independent studies have recently demonstrated loss of heterozygosity on chromosome 9p with DNA polymorphic markers in two of 27 and five of five ‘Spitz nevi’ (49,50). The latter findings corroborate the loss of chromosomal 9p with CGH and homozygous deletion of 9p21 observed with FISH.

Analysis of Gene Mutations
Recent work has shown that a series of conventional Spitz tumors and the so-called spitzoid melanomas in prepubescent children failed to show any hotspot activating mutations in the B-raf, N-ras, or H-ras genes (51). The general absence of B-raf mutations in spitzoid lesions contrasts with a high rate of mutation (53–80%) in conventional melanomas and (70–90%) in melanocytic nevi and suggests a different and perhaps yet to be characterized developmental pathway for spitzoid lesions (33).

Sentinel lymph Node Biopsy
The application of SLNB to atypical spitzoid melanocytic lesions potentially provides a means of obtaining more information about the biological characteristics of such lesions (54–57). However, upon closer scrutiny there are several fundamental questions that must be addressed before one can begin to have any meaningful data on this issue: one must have a much better understanding of the metastatic process in general versus non-malignant cellular migration and spread, and other possible explanations for the presence of ectopic cells in lymph nodes and other sites; the nature and significance of SLN deposits associated with all melanocytic lesions requires much more rigorous study and analysis; and finally, only the study of sufficient numbers of cases with long-term follow-up will provide the data to definitively know the biological nature of many SLN deposits associated with various spitzoid lesions, if they are inherently different from conventional melanomas, and if they potentially have better prognoses. Thus without such data it is impossible to know, in general, the true biological significance of spitzoid deposits in SLN. However, there are accumulating data available from the literature. Among these studies, mostly in children and adolescents, who have undergone sentinel lymph biopsy for spitzoid melanocytic tumors (probably a heterogeneous group of typical and atypical spitzoid lesions and possibly some true
melanomas), up to about 50% of patients have shown positive SLNB (57). In most instances, the tumor deposits have been microscopic and generally have involved the parenchyma or subcapsular sinuses of the SLN. With completion lymphadenectomy, only a small of percentage of patients have showed any further nodal involvement—usually only a single additional node being involved. None of the patients thus far have shown any further disease progression with follow-up ranging from months to several years (57). Although these data are preliminary and not yet conclusive due to lack of consensus interpretation of the primary spitzoid neoplasms and sufficient long-term follow-up, the patients appear to show no progression of disease and thus the positive SLN does not correlate with risk of further metastatic disease. As a result, the data suggest that many SLN deposits from spitzoid tumors appear indolent and possibly some are benign or, at least, biologically indeterminate. Consequently, atypical Spitz tumor deposits in SLNs may possibly have a different biology or significance than metastases from conventional melanoma (32–35).

Differential Diagnosis

Since we lack objective data and sufficient follow-up, the significance or weighting of the various features already mentioned has not been established. However, at present the final interpretation of a Spitzoid lesion remains almost entirely histopathologic with important consideration given to clinical information. Almost all other parameters have not yet been sufficiently studied as to have any significant impact on the final interpretation. However, some indices such as the Ki-67 labeling, CGH, and FISH may provide additional useful information in the final deliberation about a lesion. In the future, such ancillary data may take on much greater importance.

Some may point out that such an approach seems to render many or most Spitz tumors atypical. In the process of evaluating Spitz tumors common sense must prevail, and one must keep in mind that one is most likely dealing with a biological continuum with many or most Spitz tumors at the ‘benign’ or ‘less aggressive’ end of the spectrum. There is little question that as these various parameters progressively accumulate in number and severity, the probability of an aggressive phenotype or malignancy increases. It is apparent that certain parameters take on more significance than others (*represents most helpful features) (32). Potentially aggressive tumors or melanomas thus often have large size* (>5–6mm, often >10mm*); may have significant depth*; demonstrate distinct asymmetry*; poor circumscription; heterogeneity of cellular populations*; more disordered intraepidermal proliferative patterns of melanocytes without clefting; extensive pagetoid spread; irregular epidermal alterations including thinning and effacement; significant melanocytic density and confluence*; and the lack of zonation or diminished cellular density with depth (maturation)*. The lack of uniformity or homogeneity of cell type along comparable strata (from side to side) of the tumor cannot be overemphasized as a major criterion favoring melanoma. Similarly, the failure of a tumor to show progressive dispersion of melanocytes to smaller aggregates and particularly to single melanocytes (among apparently unaffected collagen bundles) in the deepest part of the lesion also suggests melanoma. Usually concurrent with depth is the uniform diminution of cellular and nuclear sizes and regular spacing of melanocytes in a Spitz nevus/tumor; the failure to observe the latter feature should prompt
consideration of melanoma. Cytologic features favoring melanoma include alterations that are a distinct departure from what is considered acceptable for a Spitz tumor*; heterogeneity of cell type throughout the lesion, particularly in an asymmetrical or haphazard pattern; high-nuclear-to-cytoplasmic ratios; granular or ‘dusty’ cytoplasm vs the ground glass cytoplasm of Spitz melanocytes; absence of delicate or dispersed chromatin patterns with thickening of nuclear membranes; a large proportion of melanocytes with hyperchromatic nuclei; and large eosinophilic nucleoli. As discussed above, the greater the absolute rate (per mm²)* and number of deeply located (dermal) mitoses*, the more evidence one has for favoring melanoma. Atypical mitoses and necrotic cells suggest melanoma, but are not absolute.

Acknowledging that this differential diagnosis is perhaps the most difficult one in melanoma pathology, there are circumstances that make it even more exasperating, if not impossible. In particular, trauma and significant host response often introduce abnormal features such as ulceration, asymmetry, heterogeneity, dermal mitoses, and cytologic abnormality suggesting the greater likelihood of melanoma. It must be kept in mind that the nuclei in Spitz tumors are delicate and that any artifact such as tissue compression or overstaining or significant host response may introduce alterations suggesting greater cytologic atypicality. In the latter circumstances, the pathologist must consider carefully all of the criteria available before rendering an interpretation. When entertaining the possibility of melanoma, one must always consider a Spitz tumor with overlapping features of pigmented spindle cell nevus/tumor and one with phenotypic heterogeneity (‘combined nevus’). Pigmented spindle cell tumors show considerable overlap with Spitz tumors and may introduce features suggesting melanoma such as greater pagetoid melanocytosis, expansile papillary dermal nests, and the absence “ground glass” cytoplasm. Spitz tumors with phenotypic heterogeneity (‘combined nevus’) may exhibit asymmetry and heterogeneity, two attributes suggesting melanoma. One must assess each component of such a lesion individually with the criteria already mentioned, and it will usually be possible to resolve the issue.

Management

All spitzoid melanocytic neoplasms should be fully resected if possible in order to facilitate complete histopathologic examination and also to diminish the risk of recurrence (32). It is clear that it will not be possible to completely resect all Spitz tumors, especially some occurring in difficult anatomic sites in children. Clinical judgment must come into play, and the risks and benefits of surgery and optimal patient care prudently assessed. Atypical spitzoid neoplasms obviously require comparable excision for the same reasons but with greater clearance (up to 1 cm) in order to provide even greater assurance that they are completely resected. The reasons for recommending excision with margins free of the tumor are that (1) Spitz tumors not completely excised have persisted (recurred) at the same site and eventually metastasized and/or death, and (2) some persistent/recurrent Spitz tumors may be more atypical than the original lesions and even more difficult to distinguish from melanoma and some have resulted in metastases. Spitzoid melanocytic tumors assigned an indeterminate biological potential probably merit surgical margins of approximately 1 cm since this is considered the minimum standard
of care for melanoma. The place of SLNB in the management of atypical spitzoid melanocytic lesions remains controversial as discussed above. Further, accumulating data suggest that the outcome from SLN biopsy may not provide any meaningful prognostic information for spitzoid lesions even if positive (32, 34, 35, 41, 54–57). Patients should be carefully monitored by regular examinations for recurrence (and metastasis in the case of atypical Spitz tumors). All patients should be managed on an individual basis and efforts made to avoid both overly aggressive and suboptimal management strategies.

Angiotropic Melanoma

The importance of angiotropism as a biological phenomenon and prognostic factor in localized melanoma and the microscopic correlate of extravascular migratory metastasis (see below) has recently been emphasized (58,59). Angiotropic melanoma is defined as the close apposition of melanoma cells to the abluminal surfaces of either blood or lymphatic channels (in a pericyte-like location), or both (Figure 17). By definition, there is no tumor present within vascular lumina. Angiotropic foci must be located either at the advancing front of the tumor or at some distance (usually within 1 to 2 mm) from the main tumoral mass. Although angiotropism is likely to be present within the mass of an invasive melanoma, there is no specific means at present to differentiate simple entrapment of vessels by tumor from angiotropism. Immunohistochemistry with markers such as S-100 protein or Melan-A/Mart-1 (Fig. 18) may aid in the identification or confirmation of angiotropism. Angiotropism is observed with greater frequency in melanomas also demonstrating neurotropism and adnexotropism suggesting closely related mechanisms. Angiotropism is observed much more frequently than vascular invasion; for example, in a series of 650 consecutive invasive melanomas, the frequency of vascular/lymphatic invasion was 1.4 percent.

Lugassy and Barnhill have proposed that an important mechanism of melanoma metastasis may be the migration of tumor cells along the abluminal surfaces of vascular channels or extravascular migratory metastasis (EVMM), a mechanism by which some tumor cells spread to nearby or more distant sites (58, 59) This mechanism of tumor spread appears to have a convincing developmental basis because of its striking similarity to the abluminal vascular migration of neural crest stem cells from the neural crest to distant sites in the embryo. Evidence for EVMM has also been based on ultrastructural, immunopathologic, and laboratory studies; in the latter, melanoma cells are closely apposed to the external surfaces of the endothelial cells of blood vessels in a pericyte-like location without evidence of intravasation (60,61). Ultrastructurally, the melanoma cells are linked to endothelium by an amorphous matrix containing laminin (not organized in basement membranes) as confirmed by immunohistochemistry (60–62) The latter morphologic structure has been termed the “Angio-tumoral Complex”. According to this proposed mechanism, tumors cells begin the process of local spread by competing with pericytes for the periendothelial position or pericyte-like location for migration along the external surfaces of vessels (58).

Clinical and Histopathologic Features

The clinical and histologic features of primary angiotropic melanoma have been delineated in a series of thirty-six cases.
The clinical findings did not differ significantly from those in a large population-based study of melanoma. All conventional types of cutaneous melanoma were observed with pagetoid, lentiginous, and nested intraepidermal components, or “nodular” morphologies. The 35 cutaneous tumors ranged in Breslow thickness from 0.46 to 8.25 mm with a mean of 1.64 mm. One patient had a mucosal melanoma involving the uterine cervix with lentiginous intraepithelial melanoma component and an extensive invasive component measuring 35 mm in thickness. All cutaneous melanomas (31/35) were level IV with the exception of two that were level II and two that were level V. Six (17%) of the tumors also showed neurotropism (58).

The prognostic significance of angiotropism as a qualitative variable, i.e., one that is simply recorded as present or absent, has recently been reported (63). A series of patients with primary cutaneous

**FIGURE 17**
Angiotropic melanoma: thin lentiginous melanoma with angiotropism of melanoma cells. Melanoma cells show close apposition to abluminal surfaces of superficial microvascular channels.

**FIGURE 18**
Angiotropic melanoma: Mart-1 highlights the angiotropic melanocytes.
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Less Common Variants of Cutaneous Melanoma

TABLE 1 Clinical and histopathologic characteristics of 36 patients with angiotropic melanoma

Angiotropism as defined above was found in patients with non-metastasizing primary melanoma and long-term follow-up.
exclusively in patients with metastasizing melanoma, and vascular/lymphatic invasion was absent. These preliminary results strongly suggest that angiotropism is an important prognostic factor correlating with metastasis, even beyond that of tumor thickness. A recent investigation has independently confirmed the importance of angiotropism as a prognostic factor in loco-regional metastasizing melanomas (64).

The prevalence of angiotropism and EVMM in melanoma metastases has been investigated in 26 patients with metastatic melanoma. Among the 26 melanoma metastases studied, angiotropism of melanoma cells was observed in some portion of the metastasis in 23 cases (65). Thirteen out of 16 in-transit metastases, all seven epidermotropic metastases, and two of three satellite metastases showed angiotropism. In general, the in transit metastases were small and some were epidermotropic while others involved solely the reticular dermis and possibly the subcutaneous fat. Melanoma cells cuffed the external surfaces of microvessels within the metastasis, at the peritumoral interface of the metastasis, or in immediate proximity to the main portion of the metastasis, in a pattern analogous to the angio-tumoral complex. The melanoma cells were present in one or more layers and occasionally in small aggregates juxtaposed to the external vascular wall. There was no evidence of intravascular involvement (intravascular invasion) in any of the 26 human melanoma metastases. Simultaneous (double) immunostaining of five specimens with S 100 protein and CD31 highlighted melanoma cell angiotropism, i.e., melanomas cells expressing S 100 were observed along the external surfaces of microvessels labeling with CD31 (65).

Management
At present there are no definitive data to suggest that melanomas demonstrating angiotropism should be managed any differently than conventional melanomas. However, with the acquisition of new research findings in large patient cohorts this may change in the future. Continued investigations are underway to define the molecular basis of EVMM and potential therapeutic avenues for intervention in the metastatic process (66–70).

BLUE NEVUS-LIKE MELANOMA
(MELANOMA ARISING IN OR RESEMBLING A BLUE NEVUS; MALIGNANT BLUE NEVUS)
Cutaneous melanoma originating from or associated with a preexisting blue nevus, commonly a cellular blue nevus (CBN), or closely resembling a blue nevus was first delineated by Allen and Spitz under the term “malignant blue nevus” (71–83). The term has not been without controversy and many have called for its abandonment. Nonetheless, this appellation continues to be used in the literature since this variant of melanoma has a unique developmental basis, i.e., origin from or resemblance to a BN, a rather distinctive clinicopathologic phenotype, and unique somatic mutations of guanine nucleotide-binding protein (GNAQ) in common with blue nevi and uveal melanoma (82). Blue nevus-like melanoma (BNLM) are extremely rare, as less than two hundred cases have thus far been reported.

Clinical Features
The average age of patients at diagnosis is in the mid-forties, about two-thirds of patients are men, and there is no predilection for any particular anatomic site, such
as the scalp as was previously thought (78, 79, 81). Blue nevus-like melanomas most frequently present as blue or blue-black plaques or nodules ranging from about 1 to 4 cm (mean: 2.9 cm) which are often multinodular. There is usually a history of recent enlargement or change in a previously stable blue nevus. Recent evidence suggests that BNLM are not more aggressive than other forms of conventional melanoma, as was previously believed; rather they are commonly diagnosed at a more advanced stage (81).

Histopathologic Features

In the most common presentations, BNLMs are often large (usually > 2 to 3 cm, range 0.5 to > 6 cm) asymmetrical nodular or multinodular tumors comprised of aggregations of spindled cells in tightly packed fascicles in the dermis and often the subcutis (Figs. 19–23) (71–75,78,79,81). In a recent large series of cases, the median Breslow thickness was 5.5 mm with a range from 1.1 to 15 mm) (81). Median Clark level was V and 26% of the BNLMs were ulcerated. By definition, there is usually sparing of the epidermis (Figure 19). Epithelioid malignant melanocytes are often a conspicuous component and useful for the recognition of BNLM. Multinucleate giant cells are also occasionally encountered. Melanin pigment and nuclear vacuolization are noted in approximately two-thirds of cases (74). Necrosis, a feature previously thought characteristic of BNLM, is observed in only about one-third of cases (74). In general, there is striking cytologic atypia, prominent nuclear pleomorphism, infrequent mitotic figures (approximately 1 to 2 but often > 5 to 6 mitoses/mm²) and, uncommonly, atypical mitoses. Most BNLM have a component of CBN, but elements of common blue nevus (pigmented dendritic melanocytes, fibrosis, and melanophages) and rarely nevus of Ota or nevus of Ito may be observed.

BNLM usually presents in one of three patterns: (1) a lesion with an overtly malignant component juxtaposed to a benign blue nevus component, usually a CBN; (2) a more subtle sarcoma-like presentation (without florid benign and malignant components) initially suggesting CBN but exhibiting large densely cellular fascicles or nodules of spindle cells that on closer inspection have sufficient atypicality for malignancy and are distinctly more abnormal than the usual small fascicular or alveolar patterns in CBN; or (3) a lesion suggesting a benign CBN with additional atypical features such as large diameter, asymmetry, prominent cellular density, nuclear pleomorphism, and some mitotic activity at least focally, but not obviously malignant, that subsequently results in malignant behavior (the authors’ term such lesions biologically indeterminate) (80).

Ancillary Techniques

Comparative Genomic Hybridization and Fluorescence In Situ Hybridization

The recently developed molecular techniques CGH and FISH appear to hold promise for their application to the difficult diagnostic problem of histologically ambiguous cellular blue nevoid melanocytic neoplasms (79, 82, 47). In particular, the distinction of CBN and atypical variants from BNLM can be one of the greatest challenges faced by histopathologists. In a recent study of cellular blue nevoid lesions assessed by CGH, all seven BNLMs showed multiple chromosomal aberrations with an average of eight per lesion as compared to none observed in 11 CBN (79). Interestingly, among 11 lesions considered to be atypical CBN, three of 11 cases
FIGURE 19
Blue nevus-like melanoma (malignant blue nevus): scanning magnification showing relatively small diameter biphasic nodular melanocytic neoplasm.

FIGURE 20
Blue nevus-like melanoma (malignant blue nevus): high magnification demonstrating hypercellular nests of heavily-melaninized atypical spindled to epithelioid melanocytes in superficial dermal portion of melanoma.

FIGURE 21
Blue nevus-like melanoma (malignant blue nevus): higher magnification of Figure 20 showing nodular component containing severely atypical spindled to epithelioid melanocytes with prominent nucleoli.
(27%) showed one to three chromosomal abnormalities, paralleling their intermediate status between conventional CBN and BNLM. The recent application of FISH with four probes targeting the chromosomal loci 6p25, 6q23, 11q23, and the centromere of chromosome 6 (Cep6) has shown relatively comparable findings (83). Five of five BNLMs demonstrated FISH abnormalities compatible with melanoma versus none observed in 12 conventional CBN. However, a recent comprehensive analysis of 575 melanocytic lesions by FISH revealed that both conventional and atypical CBNs may show comparable rates of positivity (40 to 50%) as BNLM (50%) (47).

Differential Diagnosis

The differential diagnosis of blue nevus-like melanoma includes CBN and its atypical variants, primary or metastatic melanoma, and clear cell sarcoma (76–81, 84). The
difficulty of CBN and closely-related lesions showing features that seem to deviate from the stereotypic image of CBN conceived in the literature stems from several factors: cellular blue neoplasms as a group are rare and consequently inadequate information is currently available about these lesions in general, both benign (and atypical) and malignant forms show a continuum of overlapping features; CBN may show regional (including sentinel) lymph node involvement suggesting metastatic melanoma (but not definitive evidence of malignancy); and finally, metastases may develop after the passage of long disease-free intervals, e.g., up to fifteen years in one instance. In any case, histopathologic criteria for the distinction of BNLM from CBN have been proposed in the literature. For example, as outlined above, an unquestionably malignant component often with large epithelioid malignant melanocytes juxtaposed to a bland CBN component is the single most reliable histologic criterion. Other important criteria include large size, i.e., > 1 cm, especially > 2 to 3 cm, asymmetry, multinodular configuration, mitotic rate > 2 to 3, especially > 5 to 6 per mm², atypical mitoses, zonal necrosis, nodule formation, infiltrating features, significant cytologic atypia, location on the scalp, and age beyond 45 years. Outside of exceptionally rare lesions showing overt malignant characteristics with or without a benign blue nevus remnant, the following attributes appear to lack specificity for discriminating CBN from BNLM: size, presence of mitoses (both may have fairly low mitotic rates of approximately 2/ mm²), necrosis, hypercellularity, cytologic atypia, and regional lymph node involvement. Consequently, it has been difficult to define the limits of atypicality acceptable in some percentage of CBN on the one hand and the minimal essential criteria for malignancy on the other (Figs. 41–43). As a result, an intermediate category of tumors termed “atypical blue or atypical cellular blue nevi” often with the additional qualification of indeterminate biological potential has been introduced to accommodate these controversial or borderline neoplasms (80).

Because there are no histologic features specific for BNLM, a contiguous remnant of blue nevus should be identified or a history of an antecedent blue nevus documented to distinguish BNLM from either nodular or metastatic melanoma.

Clear cell sarcoma (CCS) is distinguished by the typical clinical presentation in young adults, involvement of distal extremities, deep soft tissue involvement, typical histology, and immunohistochemistry. However, rarely CCS may present as a primary dermal neoplasm (84). If necessary, the Ewing sarcoma-cyclic AMP-dependent transcription factor (EWS-ATF-1) fusion gene in CCS can be identified through the use of RT-PCR or FISH testing.

**Prognosis**

The authors of most reported series of BNLM in the literature contend that BNLM is an aggressive neoplasm perhaps with a less favorable prognosis versus that of conventional melanoma (74). However, recent evidence from Australia argues against this commonly held belief (81). After adjustment for a more advanced stage, BNLMs appear to be no more aggressive than conventional melanomas. In this case-control study, 23 patients with BNLM were matched with a control population of conventional melanoma patients. The latter two groups were matched for age, gender, anatomic site, Breslow thickness, and ulceration. An analysis of outcomes showed that there were no significant differences between the two groups with respect to melanoma-specific mortality or
overall mortality. Further, the two groups demonstrated comparable rates (43%) of loco-regional recurrences; and, interestingly, patients with BNLMs manifested a slightly lower frequency of distant metastases compared to conventional melanoma patients. One must consider that most BNLM have been reported from large tertiary care centers with significant referral biases, most BNLM are diagnosed at an apparently advanced stage, many BNLM involve the scalp which is considered a relatively high-risk anatomic site, and it may not be possible to apply the Breslow method for measuring thickness to BNLM for comparison with conventional melanomas. Further, it is possible that pathologists have failed to recognize a subset of more indolent BNLM, i.e., those that have not shown aggressive behavior early on in their course and thus are never recognized or are diagnosed only in retrospective after the development of metastases several years later.

Management

With respect to the management of patients with MBN, there is growing evidence that the same therapeutic measures as for conventional melanoma are applicable.

COMPOSITE MELANOMAS:
MELANOMAS ASSOCIATED WITH OTHER MALIGNANT EPITHELIAL NEOPLASMS

The occurrence of cutaneous melanoma in close proximity to or within other epithelial malignant tumors is a rare and poorly-understood phenomenon which has reported in the literature over the past 30 years (85–90). The two entities most commonly associated with melanoma have been basal cell carcinoma and squamous cell carcinoma. The nature of this relationship has been the source of considerable confusion and the lack of standardized terminology. A critical analysis of the cases reported thus indicates that these tumors can more or less be categorized into four principal categories (89): 1) Collision tumors: the collision of melanoma with either squamous or basal cell carcinoma. By definition, the two neoplasms are in close proximity but maintain distinct physical boundaries; 2) Colonization of an epithelial neoplasm by melanocytes: The most common example of this is the colonization of an epithelial tumor, such as a seborrheic keratosis (melanoacanthoma), poroma, squamous cell carcinoma, basal cell carcinoma, Paget disease, etc., by benign pigmented dendritic melanocytes resulting in an appearance which simulates melanoma in situ. On the other hand, melanomas in situ may directly colonize tumors such as basal cell carcinoma, and this represents a true manifestation of composite melanoma in situ and basal cell carcinoma. 3) Combined tumors: In this circumstance, two distinct neoplasms, i.e., cutaneous melanoma, usually invasive, and another such as squamous cell carcinoma exhibit intimate intermingling of the two phenotypically different tumor cells populations. 4) Biphenotypic tumors: A malignant neoplasm comprised of tumor cells with biphenotypic differentiation, i.e., individual tumor cells show evidence of both melanocytic and epithelial differentiation (in the case of a malignant neoplasm with melanocytic and keratinocytic differentiation). To date, only extremely rare tumors have been documented to show such apparent biphenotypic differentiation in individual tumor cells by either immunohistochemistry or electron microscopy (86). The pathogenesis for such dual or biphenotypic differentiation has not been clearly elucidated.
Clinical and Histopathological Features
Since so few cases have been reported, there are no distinctive clinical or histological features apparent in the literature. As illustrated in Figs. 24 and 25, one of the most common presentations is an admixture of two distinct tumor cell populations. Immunohistochemistry is critical for the elucidation of the relationship between the two tumor cell components in such composite neoplasms (Figure 25). However, the phenotypic nature of many such unusual neoplasms may still defy easy classification. One may suspect a single line of differentiation or potentially the association of two distinct tumor cell populations as outlined in the classification above. Without sophisticated ancillary techniques such as dual immunolabeling, electron microscopy, cell culture, and molecular techniques, it may be virtually impossible to confirm whether biphenotypic malignant neoplasms with melanocytic differentiation actually exist.

FIGURE 24
Combined melanoma and squamous cell carcinoma: scanning magnification discloses a neoplasm with attributes suggesting both melanocytic and squamous lines of differentiation. An invasive melanoma of the lentigo maligna type (Breslow thickness: 3.39 mm, mitotic rate: 11 per mm², ulceration: present) is intimately admixed with a basaloid squamous cell carcinoma.

FIGURE 25
Combined melanoma and squamous cell carcinoma: expression of HMB45 in many of the same tumor cells. The same microscopic field (not shown) has demonstrated expression of cytokeratin 5/6 suggesting biphenotypic differentiation.
Differential Diagnosis

The fundamental task for the histopathologist is to verify the benign or malignant nature of the tumor and if conventional melanoma is clearly present or not. One must attempt to assign a given neoplasm into one of the categories outlined above, i.e., as a collision tumor; a tumor colonized by either benign dendritic melanocytes or melanoma cells; a combined tumor comprised of two distinct malignant cellular populations, closely intermingled but without evident biphenotypic differentiation in individual tumor cells; and finally a tumor with biphenotypic differentiation which can only be confirmed by immunohistochemistry, electron microscopy, or other advanced technique.

Prognosis

Because so few cases have been reported, because of the difficulty of classifying precisely many of these neoplasms, because of the difficulty of knowing their biological nature, and finally because of the difficulty of measuring Breslow thickness for many such lesions, there are no robust data available about the general category of composite melanomas. Nonetheless, one would presume that the major prognostic indicators for cutaneous melanoma including Breslow thickness, mitotic rate, ulceration, and stage would be applicable to these neoplasms exhibiting true biologic melanoma. Thus standardized microstaging and reporting of melanoma should be applied to composite melanomas in general.

Management

If true biologic melanoma is confirmed to be present, the same management strategy as for all conventional melanomas should be applicable.

REFERENCES


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