Nevoid malignant melanoma

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The term "nevoid malignant melanoma" (nevoid MM) is used here to describe rare nodular malignant melanomas that may escape detection in routine histological sections due to the lack of a prominent intraepidermal component, sharp lateral circumscription and evidence of partial maturation with descent in the dermis (1). Nevoid MM mimic ordinary compound or intradermal melanocytic nevi when the melanoma cells are small or Spitz's nevi when the cells are large (2, 3) (Table 1).

Reed *et at.* (4) proposed between 1975 and 1988 that two additional categories be added to the usual list of histological types of malignant melanomas, *i.e.,* minimal deviation melanoma (MOM) and borderline melanoma (4). These categories have not been generally accepted and even some of the original authors have published the recommendation that these terms be avoided (5). Other investigators have included nevoid melanomas in the category of MDM and borderline melanoma (4, 6). In contrast to "nevoid melanoma", MOM have all the heterogeneous architectural features found in melanomas in general but only less cytologic atypia (4).

Table 1. Histological comparison of nevoid melanoma and nevus.

Nevoid malignant melanoma, mall cell type	Compound nevus
Similarities	
Cells tend to be small	Cells tend to be small
Pagetoid cells are rare	Pagetoid cells are rare
Melanocytes are nested	Melanocytes are nested
Cells may disperse at base	Cells disperse at base
Differences	
Mitoses present in dermis	Mitoses absent in dermis
Nucleoli visible at base	Nucleoli inconspicuous at base
Nuclei hyperchromatic and hyperchromatic, with oval	Nuclei not very angulated at base to spindle shape at base
Pigmentation sparse	Pigmentation rare at base, present at base
HMB-45 positive at base	HMB-45 negative at base
MIB-1 positive at base	MIB-1 negative at base
Nevoid malignant melanoma, large eli type	**Spitz's nevus**
Similarities	
Cells tend to be large	Cells tend to be large
Pagetoid cells may be present	Pagetoid cells may be present
Melanocytes are nested	Melanocytes are nested
Cells may disperse at base	Cells disperse at base
Differences	
Mitoses present in dermis even at the base	Mitoses present in dermis but rarely at the base
Cell size large at base	Cell size small at base
Few Kamino bodies	Kamino bodies are common
Epidermal hyperplasis may be present	Epidermal hyperplasia is frequent
HMB-45 positive at base	HMB-45 patchy positivity and may be at base
MIB-1 undimished at base	MIB-1 diminishes to base

In 1985, Schmoeckel *et al.* (1) introduced the name "nevoid malignant melanoma" in their study of a series of 33 unusual melanomas. In their patients, 15 had developed metastases and eight had died of disseminated melanoma. These tumors were called nevoid because of certain architectural and cytologic features that strongly resembled those of ordinary benign compound or intradermal melanocytic nevi, with papillomatous or nodular shapes. Other names are preferable for those melanomas that mimic other types of nevi, for example 'superficial spreading malignant melanoma" can mimic nevi with architectural disorder or "dysplastic nevi", and "malignant blue nevus" can mimic cellular blue nevus. Certain unusual types of nevi are more difficult to differentiate from nevoid MM and include combined nevi, deep penetrating nevus (DPN) (7, 8), "atypical dermal melanocytic lesions with differentiation along schwannian lines" (9), and "dermal melanocytic tumors of uncertain potential" (10).

In our work, we have selected for study a group of unusual nevoid nodular melanomas according to the criteria of Schmoeckel *et* at. (1), including: i) lack of considerable junctional proliferation and absence of scattered tumor cells within the epidermis; ii) presence of monomorphous nevocytic tumor cells; and iii) nevoid architectural pattern, *i.e.,* poorly demarcated tumor base (often with little or no inflammatory reaction), sharp lateral demarcation, and symmetry of the whole lesion.

For immunohistochemistry, the antibodies employed were HMB-45 against a component of premelanosomes, and MIBi against the Ki-67 antigen in paraffin sections (11). The patterns of HMB-45 staining in 12 nevoid MM were compared with those in 107 melanocytic nevi, without antigen retrieval methods. HMB-45 staining was strong in the dermal component of the nevoid MM, even in the absence of a junctional component. In common acquired and congenital nevi, the upper dermal component stained less than the junctional component of the lesion. The deepest components of these nevi were negative. Spitz nevi and cellular blue nevi had positive dermal cells even without a junctional component. Additional staining for a proliferation marker, such as Ki-67 (with the antibody MIB-1 after microwave antigen retrieval), can help further in distinguishing a nevoid MM from a Spitz's nevus. Melanomas have strong nuclear staining throughout the lesion. In contrast, Spitz's nevi have more staining at the top of the lesion than at the bottom. The patterns of HMB-45 and MIB-1 staining can be used along with standard histological criteria for the diagnosis of nevoid MM, based on the detection of lack of true maturation of the tumor cells with progressive descent in the dermis. Clinical-pathological correlation is needed to distinguish some metastatic melanomas from primary nevoid MM.

It seems likely that the nevoid MM are early stages in the evolution of nodular melanomas. Often in large nodular melanomas, there are regions with different morphologies of the melanoma cells that suggest an evolution in the dermis toward a more malignant cell type (4).

Regarding prognosis, the study of Schmoeckel *et* al. (1) concluded that the clinical characteristics and prognosis of nevoid MM were similar to those of the standard melanomas and depended on the measured depth of invasion into the dermis. In other studies, there are suggestions of a better than expected prognosis for patients with nevoid melanomas (6). In a study by TY. Wong et at. (12) seven nevoid MM were reported with criteria for case selection similar to ours and a better than expected prognosis was observed. Of the 14 patients that we reported in 1995 (2), one patient was dead at 3 years; three patients with skin metastases were alive

after a follow-up of 1, 4 and 7 years; and three patients with lymph node metastases were alive after a follow-up of 6, 7 and 10 years. More patients need to be studied and followed to see if the prognosis is what would be predicted by the depth of the lesion or slightly better than that. However, there is no doubt that some patients do develop metastases and can die from such nevoid melanomas.

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Immunohistochemistry and molecular biology in the management of melanocytic lesions

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Melanocytic lesions constitute a very important part of surgical pathology material. Melanoma kills more patients than any other cutaneous malignancy and early detection is crucial in its clinical management. Additionally, melanocytic lesions are involved in a high percentage of malpractice lawsuits. Although histological exam of hematoxylin and eosin slides remains the main component in the diagnosis of melanocytic legions, in recent years, immunohistochemistry and, to a lesser extent, other molecular pathology techniques have been applied to help in the diagnosis of this group of lesions.

Immunohistochemistry

Because melanin pigment may be confused with the brown chromogen diaminobenzidine, immunohistochemical interpretation is sometimes problematic. Approaches to circumvent this problem include use of other immunohistochemical chromogens (fast red, etc.), use of Giemsa or azure B counterstain to stain melanin green, and bleaching of melanin. With bleaching techniques, reactivity for 5-100 protein, gplOO (HMB-45), the NKI-C3 antigen, CD34, and 0020 (L26) are unaffected, while certain other antigens may show enhancement or abolition. Therefore, any use of bleaching techniques in immunohistochemistry should be carefully worked up in each particular laboratory.

As in other areas of pathology, immunohistochemistry should be pertormed using a panel of antibodies to avoid misdiagnosis. For example, occasional cytokeratin expression occurs in melanoma, especially in metastases; if only anticytokeratin antibodies are used in such a case, a diagnosis of carcinoma can be entertained.

S-100 protein remains the most sensitive (if nonspecific) marker of melanocytic differentiation. Most cases initially considered 5-100-negative become positive on additional testing. In the differential diagnosis between spindle-cell melanomas and malignant peripheral nerve sheath tumors, the former usually express 5-100 protein in most tumor cells.

HMB-45 is a monoclonal antibody that detects a protein in early melanosomes. HMB-45 labels malignant melanoma of soft tissues (clear cell sarcoma), the sugar tumor" of the lung, angiomyolipomas and lymphangiomyomatosis. Because these lesions rarely occur in the skin, HMB-45 is very useful in detecting melanocytic differentiation in skin biopsies. HMB-45 labels immature or activated intraepidermal melanocytes (melanocytes of fetal and neonatal skin, proliferating melanocytes in inflamed skin or in skin adjacent to diverse neoplasms), blue nevi, the superficial portions of other nevi, and most primary melanomas. HMB-45 detects a pattern of "maturation' with labeling of the top but not of the bottom of most melanocytic nevi. Such a pattern is usually absent in melanomas, thus HMB-45 may be helpful in this differential diagnosis. The use of antigen retrieval techniques and high-sensitivity detection systems (such as streptavidin, Envision®, etc.) increases the sensitivity of HMB-45; with such techniques, up to 75% of primary spindle cell melanomas are positive, at least in a few scattered cells.

Other markers for melanocytic differentiation are under study. Peripherin, an intermediate filament involved in growth and development of the peripheral nervous system, shows a pattern of expression similar to that seen with HMB-45. Melan-A (MART-i) and tyrosinase are expressed in both nevi and melanoma. NKI-C3 is an antibody that labels melanocytic lesions as well as cellular neurothekeomas and macrophages.

The analysis of cell proliferation markers such as Ki-67 helps distinguish between benign and malignant lesions. Common, dysplastic and compound Spitz nevi exhibit reactivity in <6% of cells, generally disposed at the dermal-epidermal junction or in the more superficial dermal compartment, with an orderly gradient with progressive loss of Ki-67 expression in proportion to the dermal depth of the cells. In contrast, melanomas contain a higher count of reactive cells and do not show that orderly pattern, but instead have a random pattern of immunoreactivity. In a study with 112 lesions, the analysis of Ki-67 expression helped detect those lesions with systemic progression (recurrence or metastasis). However, in a different study, Ki-67 expression did not correlate with development of metastasis in thin melanomas. Analysis of Ki-67 expression is also