

Highlighting the immunohistochemical profile of melanocytomas (Review)

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Abstract. The histological assessment of atypical melanocytic neoplasms is mandatory to ensure proper diagnosis and treatment. However, for some atypical lesions, expert pathologists report only moderate concordance in the diagnosis. In addition, certain atypical neoplasms have been coined differently in the literature. These designations include among others atypical and metastasizing Spitz tumor, malignant Spitz naevus, borderline and intermediate melanocytic tumor, and melanocytic tumor of uncertain malignant potential (MELTUMP) or Spitzoid melanocytic tumor of uncertain malignant potential (STUMP). These neoplasms are grouped here under the heading melanocytoma. Such melanocytic lesions have a benign outcome but exhibit an atypical and worrisome aspect. Rare individual cases of melanocytomas can progress to locoregional disease (agminate melanocytomas), and even beyond. At times, the distinction between melanocytoma and melanoma is difficult and may even be impossible. However, multipronged immunohistochemistry can help define malignancy risk stratification and therapeutic guidelines.

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1. Introduction

One major expectation of patients and clinicians is to make a clear-cut distinction between benign and malignant melanocytic neoplasms. This can be reached for the vast majority of such lesions. In particular, the histological diagnosis of cutaneous melanoma is often straightforward (1). However, the situation is somewhat more ambiguous and controversial for other atypical melanocytic neoplasms. Historically, the problem was probably first raised a century ago when Darier and Civate described, in some detail, an unusual melanocytic tumor developing rapidly on the nose of a young child, and were unable to decipher whether the lesion was benign or malignant (2). At present, one can question whether dermatopathologists have made much progress in resolving this conundrum because of the inability to accurately interpret such melanocytic lesions histologically and to rate their biological potential (3).

For these unusual melanocytic neoplasms, the current histological criteria for whether they are benign or malignant are not completely met, or fail to make the distinction between benign and malignant neoplasms with confidence (4,5). Some of them may enter a spectrum going from benign to not-so-benign, not-so-malignant and malignant. Experienced pathologists commonly recognize the important microscopical features, but they may disagree with the interpretation and diagnosis (6-8).

There appears to be a trend in the literature to diagnose Spitz nevus for any problematic, probably benign, cellular junctional or compound nevus (3,9). In previous decades, the recognition of Spitz naevus variants has resulted in a marked expansion of its clinical and histological spectrum. This may risk dilution of the criteria for diagnosis of the regular Spitz nevus, which should probably remain a distinct and recognizable entity. Another trend showed that the intermediate categories between common naevi and melanomas have received various designations including among others melanocytoma, melanocytic dysplasia, deep penetrating naevus, minimal deviation and borderline melanoma, intermediate melanocytic tumor, melanocytic tumor of uncertain malignant potential (MELTUMP), spitzoid melanocytic tumor of uncertain malignant potential (STUMP), malignant Spitz naevus, metastasizing and atypical Spitz tumor, and spitzoid lesion (3,4,9-16). The profusion of all these terms may appear quite confusing. In the present review, they are grouped under the heading melanocytoma.

2. Definition of melanocytoma

Although histology is the mainstay for diagnosing atypical melanocytic neoplasms, clinical features are also of central importance and should therefore never be disregarded. Melanocytoma can be used as a single term to encompass melanocytic neoplasms which do not meet the classical histological criteria of any type of common melanocytic naevi and cutaneous melanoma (4). Melanocytoma in its strict etymological sense, implies a benign tumor of melanocytes (10). This term was initially selected to clearly separate the Spitz and pigmented spindle cell tumors (Reed naevus) from melanocytic naevi (10). This concept was further extended to a series of other atypical melanocytic lesions (4). The possible association with pregnancy and the administration of growth hormones in children of short stature has also been shown (17,18).

Melanocytomas often develop singly. Occasionally, multiple melanocytomas occur. Some of these lie grouped together (agminate type) and may arise after the removal of a solitary lesion (19).

The melanocytoma class is histologically recognized by combining certain of the following criteria: architectural abnormalities including disordered groupments of melanocytic nests, possible asymmetry, discrete nuclear atypia, anisokaryocytosis and the possible juxtaposition of an ancillary focal or diffuse inflammatory cell reaction. However, the variable combination of these signs in different lesions precludes any straightforward set of major criteria that can be used to confidently identify distinguishable subsets of melanocytomas, with the exception of the common type of Spitz melanocytoma.

Another special type of melanocytoma presents as an atypical dermal nodule in an otherwise normal-looking melanocytic naevus (3,17,20,21). Such atypical nodules may suggest an intralesional transformation, which some pathologists regard as a sign of malignancy, although it does not exhibit other features of aggressive behaviour. The increase in size of this type of melanocytic lesion is mainly due to more abundant, pale cytoplasm in each individual cell. The nuclei show only a marginal increase in size and do not exhibit pleomorphism. There may be invagination of the nucleus by cytoplasm, giving a vacuolated appearance. Mitoses are hardly ever seen.

In our experience, the overall melanocytoma F and M gender ratio was 1.6 (Table I). The age distribution was similar in the two gender groups. In general, the majority of Spitz tumors occur under the age of 20 years (3). In contrast, the incidence of all melanocytomas combined peaked in our series during the 3rd and 4th decade of life (Table I). A sharp decrease was found after the age of 50 years. Such age and gender distribution resembles what we reported for malignant melanomas (22,23).

3. Uncertainties about melanocytomas

The dichotomy between melanocytomas and malignant melanomas presupposes that all members of each group are either completely benign or fully malignant. This concept probably does not hold true. The variability in the histological

Table I. Age and gender distribution of 425 melanocytomas.

Age (years)	F	M
0-10	17	15
11-20	28	23
21-30	70	46
31-40	86	30
41-50	43	28
51-60	10	8
61-70	4	7
71-80	2	3
81-90	1	2
91-100	1	1
Total	262	163

presentations of melanocytomas poses diagnostic difficulties, particularly in the distinction with malignant melanomas (4,7,24,25). The clinical attributes may also be disturbing. Distinguishing between cutaneous melanoma, including its unusual variants masquerading as other entities and, benign lesions mimicking melanoma is one of the thorniest diagnostic conundrums for the dermatologist and the dermatopathologist (Fig. 1). Any error in this differential diagnosis has profound consequences including mutilating overtreatment or, conversely, life-threatening under-treatment. At the present time, controversies exist as to the diagnoses to be given for certain neoplasms and their predictive evolution. As a result, there is also potential implication in legal liability.

While a consensus clearly exists regarding the inadequacy of existing clinicopathological classifications and the need for additional research in this area, the empirical impressions and opinions of researchers, dermatopathologists and clinicians as to the nosology of several types of melanocytomas appear to vary widely. Even the definition of malignancy is disputed in the field of melanocytic neoplasms. There may be melanocytic neoplasms, particularly with a spitzoid aspect, that do not remain confined to the primary site. They exhibit the propensity to spread regionally in the skin (agminate type) and in the lymph nodes, but not to more distant sites. The interpretation of regional spread is subject to controversy. Certain authors regard it as formal proof of malignancy and consider the secondary lesions as satellitosis or in-transit metastases. Others argue that this stance constitutes an over-interpretation. Nonetheless, it appears that the regional cutaneous and nodal spread of melanocytomas neither equals distant metastasis nor constitutes sufficient proof of malignancy.

4. Neoplastic progression and evolution prognosis

In the context of melanocytic neoplasms, ample evidence exists of pathological, molecular and genetic aspects correlated with a gradation from benign naevi, through dysplasia and melanoma *in situ*, to invasive melanoma. This occurs firstly without metastatic potential and then with a nodular or

Table II. Primary antibodies.

Clone/ascitis	Antigen	Type and isotype	Dilution	Source
S100 a, b	S100 a, b	Pab	Prediluted	Dakopatts
A103	Melan-A/Mart-1	Mab, IgG1	1:10	Novocastra
HMB45	HMB45, gp100	Mab, IgG1, κ	1:350	Dakopatts
CD63	NKI-C3	Mab, IgG1	Prediluted	PM biomedicals
T311	Tyrosinase	Mab, IgG2a	1:25	Novocastra
MIB-1	Ki-67	Mab, IgG1	Prediluted	Immunotech
<i>Ulex europaeus</i>	<i>Ulex europaeus</i> lectin	Pab	Prediluted	Dakopatts



Figure 1. Melanocytoma of a nipple clinically mimicking a malignant melanoma of the nodular type.

vertical growth phase capable of metastasis (26-29). Despite these facts, and from clinical and histological standpoints, malignant melanoma is not one predictable disease, but exhibits a variety of different evolutive patterns. For instance, cutaneous melanoma may develop, spread widely and kill in a matter of months. However, it may remain silent in a growth-stunted phase or slowly progress for many years (30). It may also present as a smouldering disease or remain confined to a body area throughout its course. Thus, the diagnosis is often made by microscopic evaluation without, however, predicting the clinical course under the microscope with certainty. This is particularly true when dealing with the initial undistinctive stages of the malignant process. Many histological criteria have to be integrated to reach any diagnosis with confidence, but no one criterion of malignancy is absolute and can predict the evolution and outcome of the disease with certainty.

Any inflammatory infiltrate, when present, is distributed evenly throughout melanocytomas, although it may be slightly more marked at the basal and lateral sides. The presence of plasma cells highlighted by CD138 immunoreactivity should prompt a critical reconsideration of the diagnosis of melanocytoma. Similarly, signs of neoplastic regression as commonly seen in malignant melanomas are almost never encountered in melanocytomas.

Once the diagnosis of melanocytoma has been made, the question deals with the correlation of the prognosis. Immunohistochemistry remains the most common and efficient method in diagnostic and prognostic pathology. Immunohistochemical markers of melanocytic lesions have potential diagnostic and prognostic value. Unfortunately, they may bring supportive and controversial information (4,31,32). In the field of melanocytomas, four main categories of antibodies can be used for immunohistochemistry and prove to be more useful in determining their biological status (4). Our laboratory is currently using the panel displayed in Table II. The first category of immunohistological markers encompasses differentiation antibodies primarily helping in the identification of the neoplastic cell lineage and any heterogeneity in the cell characteristics. Typical antibodies of this group are directed to the S100 protein, the melanoma antigen recognized by T cells (Mart-1 and melan-A), as well as tyrosinase and its related Mel 5 protein (33). The second set of antibodies corresponds to putative neoplastic progression markers. These antibodies target gp100-HMB45 and CD63. Factor XIIIa, present in peritumoral and intratumoral dermal dendrocytes can also be investigated (34), as well as the immunohistochemical pattern of the basement membrane components (35). The third set comprises of the proliferation

MIB-1/Ki-67 marker as well as a set of antibodies exploring neoplastic apoptosis. The fourth set of antibodies encompasses *Ulex europaeus* agglutinin-1 and any other endothelial cell marker which assesses the neoplastic-related angiogenesis.

5. Melanocytoma differentiation

In general, common benign melanocytic tumors are structured in an orderly manner showing symmetry and so-called maturation with a deeper location of smaller cells inside the dermis. The immunohistochemical revelation of the differentiation markers including S100 protein and melan-A appears quite diffuse and uniform in these lesions and in most melanocytomas (4). Tyrosinase immunoreactivity decreases toward the base of most melanocytomas. In contrast, lateral asymmetry and patchy patterns of immunohistochemical differentiation are typically found in cutaneous melanomas and in some MELTUMP and STUMP as well (35).

6. Melanocytoma progression

The neoplastic progression of melanocytomas may be complex because it depends on the combination of many biological factors. Distinct profiles of molecular expressions are expected during melanocytoma progression. HMB-45 and CD63 are commonly negative in benign melanocytic nevi, but may show some immunoreactivity in triggered lesions. In melanocytomas, the pattern of positivity is characteristically superficial in location (3,4,31,36). The two markers are quite often expressed in combination in melanocytomas including MELTUMP and STUMP.

7. Melanocytoma proliferation and apoptosis

The mitotic index of the dermal component is one of the most important parameters for evaluating melanocytic lesions as increasing proliferative rates appear to correlate with the likelihood of aggressive behaviour or malignancy (37-43). Furthermore, these parameters are quantifiable. Mitoses observed in the deepest parts of the melanocytic neoplasm appear to have greater significance than more superficially located mitoses. There are no absolute thresholds for the proliferative indexes being indicative of malignancy. However, a brisk mitotic rate or Ki-67 index is not a common feature of melanocytomas, but rather suggests a malignant melanoma. In addition, the presence of abnormal mitotic figures is often indicative of malignancy. In the vast majority of melanocytomas, the mitotic index is $<6/\text{mm}^2$ and the Ki-67 index is $<5-10\%$. Higher values should prompt the revision of the diagnosis. The quantitative loss of Ki-67 expression with depth correlates with maturation and less atypical lesions (3).

Apoptosis is quite different from necrotic cell death and represents one major mechanism involved in reducing the expansile growth of melanocytic neoplasms. Melanocytic cells can undergo apoptosis resulting from the balance between the pro-apoptotic and anti-apoptotic (pro-survival) regulators. The process can be regarded as a programmed cell death which is recognized by a distinct set of morphological, biochemical and immunochemical alterations. Apoptosis is characterized biochemically by DNA fragmentation into

oligonucleosome-sized fragments. It is recognized morphologically by cell shrinking, chromatin condensation and the formation of apoptotic bodies with well preserved internal and external membranes. In most instances, apoptotic bodies are rapidly phagocytosed by adjacent cells or macrophages (33). The regulation of apoptosis not only involves a complex interaction of extracellular signals, but also the intrinsic sensitivity of a cell towards the induction of apoptosis which can be up- or down-regulated by a number of gene products.

As a functional counterpart of mitosis, apoptosis plays a crucial role in tissue homeostasis and is normally firmly regulated. Apoptosis is deranged in melanocytic neoplasms when the components and regulators of the cellular apoptotic machinery are mutated or present in inappropriate amounts (44). The pro-apoptotic factors include Bax, Bid, Fas/FasL, IFN, c-Kit/SCF, Noxa, p53, PITSRE, PUMA, TNF and TRAIL (45). The anti-apoptotic factors include Bcl-2, Bcl-XL, livin, Mcl-1, ML-LAP, NF κ B and survivin. Alternatively, other molecules including endothelins, integrins, c-Myc and TRAF-2 may show either pro- or anti-apoptotic effects (40).

8. Melanocytoma-associated angiogenesis

Microvessels have been reported to be fewer in melanocytomas than in malignant melanomas. Using antibodies to CD31 and *Ulex europaeus* agglutinin allows for a better assessment of the neoplastic vascularization (46,47). The vascular endothelial growth factor (VEGF) is frequently detectable in malignant melanomas, contrasting with the usual negativity in melanocytomas (48).

The extent of angiogenesis may help in distinguishing melanocytomas from malignant melanomas (49). However, it should be noted that some growth-stunted malignant melanomas show weak angiogenesis (30). Conversely, angiomatoid melanocytomas have been described (50).

9. Conclusion

There is increasing evidence that melanocytomas (atypical Spitz tumor, MELTUMP and STUMP) represent a type of melanocytic neoplasm distinct from common melanocytic naevi and malignant melanomas. This concept has found general acceptance. It brings greater agreement between dermatopathologists and clinicians and it supports a clearer understanding for the benefit of the patients. It remains that the distinction between atypical but benign melanocytic neoplasms and malignant melanoma may prove to be difficult and even practically impossible in certain instances. The discrimination between these neoplasms is subject to substantial interobserver variation. Thus, the interpretations of the observations are complex and may remain inconclusive. As a consequence, the terms melanocytoma, atypical Spitz tumor or MELTUMP and STUMP are now used for lesions somewhat resembling Spitz tumor, but with additionally worrying features. The use of the melanocytoma concept makes a diagnosis out of what is essentially a statement of uncertainty. Nevertheless, there is a group of lesions for which the current histological criteria of melanocytoma and of melanoma do not permit a confident and unequivocal diagnosis. Based on our experience, immunohistochemistry

improves the distinction between melanocytomas and melanomas more than other additional techniques. Although the data are in need of independent confirmation, there is reason to hope that some of the parameters put forward will prove to be robust and applicable in a routine diagnostic setting.

Much remains to be learned about melanocytomas. Further study of the melanocytoma spectrum by means of various additional techniques holds promise for a gradual increase in diagnostic accuracy in the future. Detailed and precise long-term follow-up of regional and distant metastasis and of neoplasm-related death must remain the mainstay of definitive classification and of the corroboration of diagnostic applicability of any offered diagnostic clue or parameter.

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