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Mini Review

Cutaneous Melanocytomas: Variants and Caveats

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Abstract

There is a regular improvement in the early clinical disclosure of various atypical melanocytic neoplasms (AMN). The histopathological examination of AMN remains mandatory for establishing their diagnosis and proper management. Panels of experts in AMN diagnosis report only moderate agreement in a diversity of puzzling cases. Some AMN have been differently designated in the literature including atypical Spitz tumor, metastasizing Spitz tumor, borderline and intermediate melanocytic tumor, malignant Spitz nevus and pigmented epithelioid melanocytoma or animal-type melanoma. Some acronyms have been further offered such as MELTUMP (after "melanocytic tumor of uncertain malignant potential") and STUMP (after "Spitzoid melanocytic tumor of uncertain malignant potential"). In this review, such AMN at the exclusion of cutaneous malignant melanoma (MM) variants, are grouped under the tentative broad heading cutaneous melanocytoma. These lesions typically follow an indolent course, although they exhibit an atypical and sometimes worrisome patterns or cytologic aspects. Rare cases of cutaneous melanocytomas progress to locoregional clusters of lesions (agminate lesions), and even to regional lymph nodes. At times, the distinction between a cutaneous melanocytoma and MM remains problematic and even proves to be merely impossible. However, multipronged immunohistochemistry helps assessing the malignancy risk.

Keywords: Malignant melanoma; Cutaneous melanocytoma; Pronostic factor; Risk stratification; Spitzoid tumor; Immunohistochemistry; Cell proliferation

Introduction

Over the past decades, the worldwide incidence of sporadic cutaneous malignant melanoma (SCMM) has considerably increased in Caucasian populations [1-4]. In this perspective, there is growing need to improve diagnostic procedures supporting early treatment and decreasing SCMM morbidity and mortality.

SCMM are in part classified according to its clinical growth rate. Fast-growing SCMM are typically characterized by a vertical growth pattern. They have a worse prognosis compared to slow-growing SCMM which are commonly confined superficially [5,6].

In most instances, the histopathological presentation of SCMM is straightforward for experts in the field [7]. SCMM are classified according to the total thickness of the primary tumor, the proliferative activity, the presence of ulceration, the tissue level of penetration depth, and the identification of metastases. However, due to the wide spectrum of histological features the situation occasionally appears ambiguous [8,9]. For instance, in small size melanocytic lesions, all the classical histological criteria for borderline SCMM or undisputable SCMM are not always met, or they fail to make the distinction confidently. Those neoplasms are tentatively classified in a spectrum of atypical melanocytic neoplasms (AMN) encompassing intermediate categories [10-19] variously referred to as cutaneous melanocytomas, melanocytic dysplasia's, minimal deviation melanomas, borderline melanomas, melanocytic tumors of uncertain malignant potential (MELTUMP) and spitzoid melanocytic tumors of uncertain malignant potential (STUMP) [20].

Although conventional histology is the mainstay for diagnosing AMN, clinical features, in particular the dermoscopic aspects remain of central importance. Cutaneous melanocytoma in its strict etymological sense, refers to benign tumor of melanocytes [10,19]. This term encompasses melanocytic neoplasms which do not meet the regular histological criteria of any specific type of common melanocytic naevi and SCMM [15,19]. They often develop singly, but occasionally, multiple cutaneous melanocytomas occur. Some of these lie grouped together (agminate type) and potentially recur after removal of a solitary lesion [14,21]. The term melanocytoma is similarly used in other fields of human pathology (leptomeninges, eye) and animal pathology (skin) for distinguishing peculiar and usually benign melanocytic neoplasms [22-24].

The recognition of intermediate sets of AMN and a better molecular staging of SCMM types has benefited from progresses in immunohistochemistry [25,26]. Using such an approach, most uncommon SCMM variants are identified with confidence [9,12,13]. It is acknowledged that SCMM molecular alterations and their respective immunological responses accompany the neoplastic progression from incipient to advanced stages. In this field, it is possible to use markers of proliferation, melanocytic differentiation and immunomodulation. In addition, the identification of signalling molecules, nerve growth factors and receptors is potentially useful, particularly in spindle cell variants of SCMM.

Triggered melanocytic naevi and cutaneous melanocytomas

In a series of endogenous and exogenous conditions,

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melanocytic naevi are triggered and some of them appear as cutaneous melanocytomas. A set of specific internal messages and environmental factors have been identified in this field. Examples are cutaneous melanocytomas developed on congenital nevi, dysplastic nevi [27], nevi modified by pregnancy or hormonal contraception [28], nevi of subjects on growth hormone therapy [11], nevi under ultraviolet-light irradiation [29,30]. It should be mentioned that some of these lesions mimick SCMM or are at risk for MM development. The possibility of a cutaneous melanocytoma should be evoked in each single case. In this review, the term cutaneous melanocytoma encompasses a broad category of melanocytic neoplasms that are further distinguished according to the identified origins and the clinico-pathological confrontation.

Globally, the cutaneous melanocytoma class is histologically recognized by the combination of some criteria including architectural disorganisation and asymmetry, discrete nuclear atypia and anisokaryocytosis, as well as the eventual juxtaposition of an ancillary focal or diffuse inflammatory cell reaction. However, the variable combination and extent of such signs in different lesions preclude establishing any straightforward set of major criteria identifying distinct specific subsets of cutaneous melanocytomas, with, however, the exception of the common type of Spitz melanocytoma (nevus).

Another special type of cutaneous melanocytoma presents as an atypical dermal nodule in an otherwise normal-looking melanocytic nevus. Such atypical nodules suggest an intralesional transformation recognized by some pathologists as a sign of malignancy, although it does not exhibit other features of aggressive behavior. 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. Invagination of the nucleus by cytoplasm possibly occurs, giving a vacuolated appearance. Mitoses are hardly ever seen.

After excluding the pregnancy-related changes in melanocytic lesions, the overall cutaneous melanocytoma gender ratio (F/M) is about 1.6 [19]. The age distribution is similar in the both gender groups. The prevalence of all melanocytomas peaks during the 3rd and 4th decades of life and a sharp decrease occurs after the age of 50 years on. Such age and gender distributions resemble that of SCMM [15].

The distinction between cutaneous melanocytomas and SCMM ideally expects that all members of each group behave either completely benign or fully malignant. This concept probably does not fully hold true. The variability in the histopathological presentations of SCMM and cutaneous melanocytomas poses diagnostic difficulties and the clinical attributes occasionally remain disturbing. 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 leading to potential implication in legal liability.

Microscopic presentation of cutaneous melanocytomas

The distinction between cutaneous melanocytomas and SCMM presupposes that all members of each group are either completely benign or fully malignant. Such a concept probably does not hold true. The histopathological variability of cutaneous melanocytomas implements diagnostic difficulties, particularly in the distinction with SCMM. In some instances, the clinical aspects are similarly disturbing. Distinguishing, on the one hand, SCMM including its unusual variants masquerading as other entities and, on the other hand, benign lesions mimicking SCMM is one of the thorniest diagnostic conundrums. A mistake in this differential diagnosis leads to profound consequences including mutilating overtreatment or conversely life threatening under treatment. At present, controversies exist as to the diagnoses given to some neoplasms and their predictive evolution. As a result, there is potential implication in legal liability.

A consensus clearly exists regarding the inadequacy of some current clinico-pathologic classifications and the need for additional research in this area. Any empiric statement and dogmatic opinion in the fields as to the nosology of several types of cutaneous melanocytomas seem to vary widely. Even the definition of malignancy is disputed in the field of AMN. Some AMN, particularly those with an atypical spitzoid aspect, do not remain confined to the primary site. They exhibit the propensity to spread regionally in the skin (agminate type) and possibly to the regional lymph nodes [17], but not to further distant sites. The survival rate appears unaffected by such regional progression.

The interpretation of regional spread is subject to controversy. Some authors regard it as a formal proof of malignancy considering the secondary lesions as satellitosis or in-transit metastases. By contrast, others argue that this stance constitutes an overinterpretation. Nonetheless, any regional cutaneous and nodal spread of cutaneous melanocytomas is not similar to distant metastasis to internal organs and does not constitute a definitive proof of malignancy.

For a series of AMN, the current histopathologic criteria for benignancy or malignancy are not fully met or fail to make the distinction between these two basic conditions with confidence. Some differentiation markers are routinely used when facing an atypical melanocytic neoplasm. Immunohistochemistry is used as an adjunct for distinguishing SCMM and cutaneous melanocytomas or other neoplasms. The common antibodies are directed to the S100 protein, the gp100/HMB45, the melan A/MART-1, the CD63/NKi-C3 and tyrosinase [31].

In general, the common benign melanocytic neoplasms are structured in an orderly manner showing symmetry and so-called maturation with deeper location of smaller cells toward the base of the lesion. In general, the sensitivity of the differentiation markers decreases or becomes heterogeneous in SCMM with increasing clinical stage including metastatic lesions [32]. Such a feature is not found with maturation of cutaneous melanocytomas. It should be mentioned that immunohistochemistry proved to be very useful in tracking SCMM microsatellites [33] which are predictors of sentinel lymph node metastases and relapse-free survival [34].

Growth fraction, proliferation and apoptosis in cutaneous melanocytomas

The disturbance of autonomous growth regulatory pathways in melanocytomas and SCMM appears to be of prime importance. Atypical tripolar mitotic figures were indicative for SCMM rather than cutaneous melanocytomas. Autoradiography after

incorporation of tritiated thymidine [33] revealed a positive correlation between the ^{3}H-TdR labeling index and the SCMM thickness. Metastases remained with a high immunolabeling index while benign melanocytic lesions showed a very low proportion of cells in S phase. As the radioautography procedure was almost impossible to apply routinely, the method was switched to the Ki67 immunolabelings which brought similar information. There are two clinical applications for which these markers have been studied, namely the distinction of melanocytic naevi from SCMM and the assessment of clinical prognosis for patients with SCMM.

The most widely used proliferation marker is Ki67, a nuclear antigen present in all active phases of cell cycle proliferation (G_1, S, G_2 and M), but absent in the quiescent phase (G0) [34]. Ki67 immunolabeling has been shown to be positive in <5% of cells in most melanocytic nevi. Up to 15% positivity may be found in cutaneous melanocytomas [35,36]. The quantitative loss of Ki67 expression with depth correlates with maturation and less atypical lesions [12,37]. A brisk mitotic rate or Ki67 index is not a common feature of cutaneous melanocytomas, but rather suggests SCMM. Most thin SCMM appear to be in a growth-stunted phase exhibiting an accretive rather than proliferative formation of nests. Thicker SCMM and their metastases have a higher Ki67 index. On the overall, the Ki67 index reaches 15-30% of SCMM cells although some individual cases show much more nuclear positivity. The Ki67 index alone is not a reliable discriminator between SCMM and cutaneous melanocytomas when it ranges in the overlap 10-20%. The presence of SCMM stem cells (low Ki67 index) [38] and clonal events [39] further complicate the process [40].

In our experience, the Ki67 index of keratinocytes is often higher than that of tumoral cells in cutaneous melanocytomas. The reverse situation is seen in SCMM thicker than 0.4 mm.

Apoptosis is different from necrotic cell death and represents one major mechanism involved in reducing the expansible growth of melanocytic neoplasms. As a functional counterpart of mitosis, apoptosis plays a crucial role 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. The pro-apoptotic factors include among others Bax, Bid, Fas/FasL, IFN, c-Kit/SCF, Noxa, p53, PITSLRE, PUMA, TNF and TRAIL. The anti-apoptotic factors include Bcl-2, Bcl-XI, livin, Mcl-1, ML-LAP, NFkB and survivin. Alternatively, other molecules including endothelins, integrins, c-Myc and TRAF-2 show either pro- or anti-apoptotic effects [41].

Apoptosis commonly appear quite active in cutaneous melanocytomas. The so-called Kamino bodies in Spitz melanocytoma likely result from such a process. At present the complex machinery of apoptosis has not been thoroughly studied in cutaneous melanocytomas.

Microvasculature of cutaneous melanocytomas

In thin MM, the microvascular density shows a wide range of development among distinct lesions. An overall stochastic relationship appears to be present between the microvasculature size and the size of the germinative compartment.

Microvessels have been reported to be fewer in cutaneous melanocytomas than in SCMM. The vascular endothelial growth factor (VEGF) is frequently detectable in SCMM, contrasting with the usual negativity in cutaneous melanocytomas.

The extent of angiogenesis may help in distinguishing cutaneous melanocytomas from SCMM. However, it should be noted that some growth-stunted SCMM show weak angiogenesis [42]. Conversely, angiomatoid cutaneous melanocytomas have been described [43]. Therefore, the differences in SCMM and cutaneous melanocytoma angiogenesis seem to be more statistically significant than clinically useful due to the extensive overlap in extent from any case to case.

Conclusion

Melanocytic neoplasms of the skin are heterogeneous in nature and in aspect. A vast number of genetic changes are described in SCMM, but the primary ones are not clearly defined. Cutaneous melanocytomas represent benign melanocytic neoplasms showing atypical features at the histological inspection. However, there is no single criterion defining cutaneous melanocytomas. The distinction between malignant melanoma and cutaneous melanocytomas is of utmost importance for the management of patients. The combination of moderately increased cell proliferation and heterogeneous patchy differentiation is a clue for cutaneous melanocytomas irrespective of their type. Most cutaneous melanocytomas appear to result from the effect of some internal or extrinsic triggering factors.

Traditional classification systems for SCMM have centered on clinicopathological correlations. Although some particular SCMM subtypes are clinically and histologically distinct, a wealth of studies indicates that current parameters for classification are without independent prognostic value. Indeed, some markers of potential clinical utility looking promising in small-scale studies fail to prove clinically useful in larger-scale studies. Such disappointing features appear to stem from the heterogeneous nature of SCMM during its evolution. A vast number of molecular changes are indeed present in advanced SCMM compared with melanocytes. Various mutations are disclosed from comparative gene expression profiling of SCMM from different stages. It is difficult to sort out which are central to malignancy and typical for SCMM. In the wide range of molecular changes it is therefore difficult to sharply define when a given melanocytic neoplasm becomes malignant. In this context, cutaneous melanocytomas are part of an evolving paradigm for classifying melanocytic neoplasms.

Cutaneous melanocytomas form an intermediate category of melanocytic neoplasms between common naevi and SCMM. They behave as benign lesions but their histological presentations may be troublesome or worrying. Immunohistochemistry evaluating differentiation markers and proliferation markers helps distinguishing cutaneous melanocytomas from SCMM. A multipronged immunohistochemical analysis should be performed in order to reach a high level of diagnostic accuracy.

We underscore recent studies that have provided insights into the diversity of melanocytic neoplasms. We expect these studies and subsequent analogous studies will inform the melanoma research community and the dermatologist as well in novel ways to manage patients with atypical melanocytic neoplasms.

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