Simulants of malignant melanoma

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Abstract

During the recent period, dermoscopy has yielded improvement in the early disclosure of various atypical melanocytic neoplasms (AMN) of the skin. Beyond this clinical procedure, AMN histopathology remains mandatory for establishing their precise diagnosis. Of note, panels of experts in AMN merely report moderate agreement in various puzzling cases. Divergences in opinion and misdiagnosis are likely increased when histopathological criteria are not fine-tuned and when facing a diversity of AMN types. Furthermore, some AMN have been differently named in the literature including atypical Spitz tumor, metastasizing Spitz tumor, borderline and intermediate melanocytic tumor, malignant Spitz nevus, pigmented epithelioid melanocytoma or animal-type melanoma. Some acronyms have been further suggested 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 *skin melanocytoma*. Such set of AMN frequently follows an indolent course, although they exhibit atypical and sometimes worrisome patterns or cytological atypia. Rare cases of skin melanocytomas progress to loco regional clusters of lesions (agminate melanocytomas), and even to regional lymph nodes. At times, the distinction between a skin melanocytoma and MM remains puzzling. However, multipronged immunohistochemistry and emerging molecular biology help profiling any malignancy risk if present.

Introduction

In recent times, a progressive pace of changes took place in the incidence of cutaneous malignant melanomas (MM) mostly affecting Caucasian populations everywhere in the world.[1] The observed rising MM incidence was probably inflated by thorough clinical screenings using dermoscopy disclosing more small size MM. The fear of this malignancy exerts a major impact in the relationship between patients, dermatologists and dermatopathologists. In connection with the medico-legal liability, the risk of overcalling or conversely minimizing some disturbing lesions is a matter of concern. The histopathological identification of MM is commonly undisputed for most expert dermatopathologists.[2] However, the diagnosis is occasionally less straightforward and remains controversial for some distinct atypical melanocytic neoplasms (AMN) of uncertain prognosis.[3-5] Dysplastic nevi are important simulants of MM. Clinical and histopathological criteria for diagnosis have been clearly delineated for dysplastic nevi. A remarkable consensus prevails about the presence of dysplastic nevi as risk markers for familial MM.[6] The size of dysplastic nevi is larger than common nevi. They show clinical asymmetry. Some color variegation and a hint of border irregularity are commonly present. Criteria overlap to some extent between enlarging dysplastic nevi and signs of the radial growth phase of MM. The aspect of dysplastic nevi evolves over time, usually in the direction of greater cell compactness. Contrasting with MM, there is no evidence for partial regression in dysplastic nevi. The *ugly duckling* aspect of dysplastic nevi evoked at the clinical inspection is commonly adequately interpreted at dermoscopic and cyanoacrylate skin surface stripping examinations.[7] The regular histopathological examination represents the final *gold standard* for ruling out MM in a concerned lesion. For a series of other AMN, the current histopathological criteria for benignancy or malignancy are not fully met or fail to make a sharp distinction between MM and AMN with confidence.[8] In fact, AMN encompass indolent, low-grade, but occasionally seemingly looking as median-grade, and exceptionally high-grade lesions. Experienced dermatopathologists commonly recognize the major microscopic features, but some experts in the field occasionally question the interpretations given to findings and the diagnostic proposals.[4] In this state of uncertainty, a few case reports have yielded borderline AMN, but later showing metastases leading to death. This created a matter of confusion and controversy. In many instances, such lesions were not scrutinized using forefront immunohistochemistry. As described below, such laboratory procedure usually highlights distinct aspects about the biology and growth patterns linked to the potential evolution of AMN.

Quandaries about atypical melanocytic neoplasms diagnosis

A clear laboratory distinction is expected between MM and melanocytic nevi, although it not always fulfilled. Some quandaries

about MM and AMN diagnosis remain complex and puzzling. The problem was probably first raised in the literature about one century ago when two French dermatologists, J. Darier and A. Civatte, described in minute detail a worrying melanocytic tumor.[9] The lesion was reported to growth rapidly on the nose of a child, and both dermatologists were thwarted in their efforts to rule on the benign or malignant nature of the tumor. About four decades later, a new concept emerged following observations made by S. Spitz who pointed to *melanomas following a benign course* in young subjects.[10] Since that time, the borderline between Spitz tumors and MM remained uncertain in some instances.[11-15]

Other melanocytic tumors exhibit atypical features somewhat mimicking MM. In some cases, a variety of triggering factors were identified.[16-21] Presently, it remains that little progress has been performed in identifying AMN etiologies because of the inability to accurately interpret the histopathology and the biological potential of a set of lesions. Future works on molecular biology will probably bring some insights in this field.[22]

In the current literature, Spitz tumor and its variants showed a marked expansion among the clinico-pathological AMN spectrum. As a consequence, there is a risk of loosing specific diagnostic criteria for the typical Spitz tumor, which should remain a distinct and recognizable entity. As another trend, the other groups of AMN have received various designations. They include pigmented epithelioid melanocytoma, melanocytic dysplasia, deep penetrating nevus, minimal deviation MM, borderline MM, intermediate melanocytic tumor, melanocytic tumor of uncertain malignant potential (MELTUMP), spitzoid melanocytic tumor of uncertain malignant potential (STUMP), malignant Spitz nevus, metastasizing Spitz tumor, atypical Spitz tumor, spitzoid lesion and still other denominations.[8] The profusion of all these terms potentially appears quite confusing. In the present work, the atypical but indolent AMN variants are tentatively grouped under the global heading skin melanocytoma.[8]

Skin melanocytoma in clinical perspective

Of note, the term melanocytoma was introduced in human pathology (leptomeninges, eye)[23,24] and animal skin pathology[25-27] distinguishing atypical but usually benign melanocytic neoplasms. There is mounting evidence that skin melanocytomas represent neoplasms distinct from common melanocytic nevi and MM. Such a distinction has found general acceptance on a descriptive morphological level. It supports a clearer understanding for the benefit of the patients. It remains that the distinction between AMN and MM is occasionally difficult, and even impossible. It remains that specific skin melanocytoma gene mutations have not yet been identified. Some of them are possibly involved in melanocytic nevus formation.

Human histopathology presently represents the mainstay for routine identification of AMN. Clinical features remain, however, of major importance, and should not be disregarded. The term skin melanocytoma is used as an overall term encompassing AMN which do not meet the regular histopathological criteria of any recognized type of melanocytic nevus and MM.[8,28] Such melanocytoma was initially selected in human dermatopathology for distinguishing Spitz tumor and the pigmented spindle cell tumor (Reed nevus) from regular melanocytic nevi.[28-30] Such a concept was further extended to a set of other AMN.[8]

Under diverse internal and external conditions, melanocytes and nevocytes are possibly triggered, and some of them form skin melanocytomas. A few specific endogenous (endocrine) messages, genetic influences and environmental factors were identified in this field. For instance, some skin melanocytomas develop on congenital and dysplastic nevi,[31] melanocytic nevi modified by pregnancy or oral contraception,[21,32] some nevi of subjects on growth hormone therapy,[16] melanocytic nevi transitorily modified under ultraviolet-light irradiation.[33,34] The possibility of a skin melanocytoma should be evoked in any of each single cases. Some of them represent an atypical progression step in the maturation of an otherwise benign melanocytic neoplasm. In humans, skin melanocytomas often occur singly. Occasionally, a clusters of melanocytomas develop.[18] Some of these lesions are clustered (so-called agminate AMN) and arise incidentally after removal of a solitary lesion.[19]

MM is more common in fair skinned Caucasian subjects.[35,36] A similar epidemiology for AMN supports the role of skin color as a risk factor for such benign neoplasms. In Caucasian populations, sunburns and sharp episodes of intense sun exposure during childhood were more associated with relative MM risk compared to cumulative lifetime exposure.[37] The risk associated with sun exposure is no longer significant once adjusted for the ability to tan and/or susceptibility to sunburn defined in the Fitzpatrick skin types.[38,39] Sunburns have been associated with MM, but the relative risks are low, around 1.5.[36] Currently, there is no report pointing to a causative relationship between intense or chronic sun exposures and skin melanocytomas.

Different *at risk phenotypes* are associated with MM. The most powerful predictors for MM are a high number of melanocytic nevi or, alternatively, recurrent photodamages with actinic keratoses. The number of melanocytic nevi appears to be the strongest risk factor for MM with an odds ratio in the order of 5 to 10, which is far greater than the relative risk for MM associated with sun exposure.[40-43] The risk factors associating MM with an excess of melanocytic nevi is consistent across the world, even with variable levels of sun exposure.[43] There are no significant differences in the magnitude of relative risks for MM in relation to the number of nevi when comparing Australia and Europe findings.[40-43] By contrast, skin melanocytomas are not linked to any of these risk predictors.

The evolution of MM discloses the relative contribution of genetics and environmental impact in the set of risk factors. Mean age at diagnosis, body distribution of MM according to gender are similar among different Caucasian populations. MM sites in both genders are different with women more likely to have MM on the lower legs whilst men are more likely to have MM on the trunk.[44] Such gender difference is similar across all latitudes showing that the extent in sun exposure does not really affect body site MM locations, and that other genetically determined gender-related factors affect MM.

In our experience, the overall F/M sex ratio of skin melanocytomas reaches 1.6 or so.[8] The age distribution looks similar in both genders. In general, most Spitz tumors occur before the early twentieth. By contrast, the prevalence of the other skin melanocytomas peaks during the 3rd and 4th decade of life. A sharp decrease is found after the age of 50 years. Such age and gender distributions somewhat resemble that of MM.[1]

Skin melanocytoma: a simulator but not a precursor of malignant melanoma

For laypeople facing an AMN, there is commonly a lack of distinction between the diagnosis and the expected outcome prediction. The diagnosis of MM is much more frightening than AMN diagnoses which are perceived as reassuring. However, a gray area exists between the recognizable truly benign melanocytic neoplasms and MM. Diagnostic disagreement is not exceptional among experts in both the clinical and histopathological fields.[4] The clinico-pathologic correlation remains of importance in the diagnostic and prognostic evaluations of melanocytic tumors.

Prognostic factors associated with AMN correspond to selective cri-

teria with expected reliability. As such, some biological factors recognized to influence the neoplastic progression are frequently skipped when providing a diagnostic opinion. Thus, there are possibly subsets of non-metastasizing MM, as well as nevoid MM simulating benign lesions and MM simulants. Clearly, some molecular and biological features do not match exactly with the diagnosis stemmed from standard microscopy of AMN. Some borderline AMN lesions give rise to metastases in a minority of patients. Hence, misdiagnosis, but also some currently unpredictable natural outcomes, scientific uncertainties about cancer progression, and practical limitations in the routine laboratory practice concur to create a gap between the histopathological diagnosis and the expectation of an accurate prognostic determination.

The discrimination between the diversity in these neoplasms is hampered by interobserver variations in the interpretation of morphological aspects of AMN. Thus, the descriptive interpretations are occasionally uncertain. The concept of skin melanocytoma is thus applied to AMN looking like a Spitz tumor, but with variable atypical histopathological presentations. It remains that a group of AMN that does not exhibit the current histopathological criteria of skin melanocytoma or MM, do not allow an unequivocal diagnosis with confidence. From personal observations, immunohistochemistry helps distinguishing skin melanocytomas from MM.[8] Although data need further independent confirmation, some of the parameters put forward prove to be robust and applicable to routine diagnostic settings. Much remains to be learned about the skin melanocytoma spectrum. Further studies should gradually increase the diagnostic accuracy in the future.

The most promising diagnostic immunopathological clues for distinguishing AMN from MM appear to be some immunostaining patterns in nests of neoplastic cells with a given differentiation antibody. Of note, uneven immunohistochemical patterns of neoplastic progression markers are encountered in both skin melanocytomas and triggered melanocytic nevi as well.

What next?

At this stage of conceptual consideration, MM are morphologically distinct from the group of AMN. Various morphological presentations of AMN are described with a common biological evolution. The AMN tentatively gathered as skin melanocytomas cannot be defined by specific morphological criteria, except that do not show those of MM. The most typical exclusion criteria for benign AMN are a lack of cell maturation, and presence of atypical and deep mitoses. By contrast, nuclear pleomorphism and high nuclear-cytoplasmic ratio, and numerous so-called Kamino's bodies are quite common in skin melanocytomas. A large germinative compartment (high Ki-67 index) is occasionally present.

In the current literature, there is a lack of reports on a single major genetic mutation defining any AMN. None of those that are identified in MM are apparently expressed in AMN. It is, however, possible that some genes regulating the cell cycle of proliferation should be involved at some stages of AMN.

By and large, the AMN spectrum exhibits a variety of clinical and histological presentations that are unified by a similar biological issue. The AMN do not seem to be influenced by genders and a specific environmental factor including sun exposures. General practitioners are potentially at the frontline for early diagnosis. The global management of the patient does not require a large and deep excision and a medical follow-up.

The contribution of surrogate markers in the AMN diagnosis remains to be scrutinized.[8,27] A reduced expression of glutathione-S-transferase has been documented in pigmented epithelioid melanocytomas.[45] This enzyme is a detoxifying agent,[46] involved in tumor progression. A distinct potential means distinguishing various skin melanocytomas and MM relies on their distinct expression of the −1 and −5 type IV collagen surrounding the tumoral nests.[47] Still another clue is possibly represented by the immunohistochemical expression of disturbed *HOX* gene products.[48]

Molecular biology opens novel methods in the diagnostic field of skin melanocytomas.[49] At present, fluorescence *in situ* hybridization (FISH) testing was used in lesions with borderline morphologies[50,51] showing molecular complexity and a variety of mutations. The chromosomal G banding testing will probably provide superior information to FISH for classifying skin melanocytomas and other AMN.[52-54] In this field, validations against clinical presentations and evolutions are expected in the future. Many of the early morphologic MM types correlate with dominant mutations. In a near future, it is expected that some AMN types will reveal mutations involved in stratifying risk, and will help to identify some indolent skin melanocytomas.[55]

Conclusions

Skin melanocytomas represent a category of melanocytic neoplasms on the borders between common melanocytic nevi and MM. They often represent benign lesions with spontaneous limitations in both their size and propensity for tissue invasion. However, their histopathological presentations are commonly troublesome, and even worrying. Selected immunohistochemistry helps for diagnostic and prognostic purposes in melanocytic neoplasms. Information should be gathered from a panel of antibodies in order to increase relevance of the findings and to reduce part of the uncertainties. In particular, immunohistochemistry evaluating the maturation and proliferation markers helps distinguishing skin melanocytomas from MM. Multipronged immunohistochemistry and DNA molecular biology should be performed in order to increase the diagnostic accuracy.

Recent studies underscore the diversity of AMN. Such observations, and any subsequent analogous research, will improve the ways to manage patients with AMN. By spreading the knowledge of skin melanocytoma variants, larger series of cases should be collected in the coming years, making it possible to better determine the clinicopathological characteristics of these tumors. It would be important to fine-tune specific (immuno-) histopathological aspects of skin melanocytomas. An accurate follow-up of large series of cases will allow to better defining the frontier between MM and indolent skin melanocytomas. Further studies are still required to perceive and understand the etiology, the risk factors and the best way to deal with skin melanocytomas. Ultimately, bioactive compounds and topical pharmacologic agents blocking any agent (growth factor, hormone) responsible for the skin melanocytoma genesis and growth should be searched for.

It remains that in rare cases the distinction between skin melanocytomas and MM proves to be difficult to establish. The prognosis is then unpredictable and unclear. Future cytogenetic studies could possibly uncover and help understanding the behavior of skin melanocytomas.

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