Published in final edited form as:

J Cutan Pathol. 2012 January ; 39(1): 21–24. doi:10.1111/j.1600-0560.2011.01849.x.

An atypical melanocytic lesion without genomic abnormalities shows locoregional metastasis

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Abstract

A subset of difficult melanocytic lesions exists with histopathologic features that evade diagnostic consensus from even expert dermatopathologists. Comparative genomic hybridization (CGH) has emerged as a useful diagnostic tool to categorize these lesions, by identifying known chromosomal aberrations in malignant melanoma the lack thereof in melanocytic nevi. However, determining a lesion's biological behavior primarily on CGH is limited by a relatively small series of corroborative cases without long term follow up. We present case of a pigmented lesion on the right cheek of a 4 year old boy. The lesion had features of a deep penetrating nevus, but the presence of frequent mitoses, tumor infiltrating lymphocytes, and microscopic foci of tumor necrosis were concerning for an unusual melanoma. We termed this lesion a melanocytic tumor of uncertain potential (MELTUMP) for these reasons. High-resolution array-CGH performed elsewhere on the lesion demonstrated no melanoma-associated genomic abnormalities. A sentinel lymph node biopsy of this patient later revealed multiple small tumor deposits. Although the presence of nodal involvement in similar lesions often do not lead to progressive and fatal disease, this case illustrates that atypical melanocytic lesions with nodal involvement may not demonstrate genomic abnormalities by CGH, and that histopathologic assessment remains paramount in defining these difficult melanocytic lesions. Further comprehensive study of these lesions is needed.

Keywords

atypical Spitz tumor; deep penetrating nevus; melanoma; melanocytic lesion; melanocytic tumor of uncertain malignant potential

Certain melanocytic lesions obscure the boundary between conventional melanocytic nevus and melanoma and have long perplexed dermatopathologists because of their morphology and biologic behavior, often eluding consensus in their diagnosis as well as their nomenclature.^{1,2} Characterized as 'borderline melanomas', 'minimal deviation melanoma' and 'atypical' counterparts to conventional melanocytic proliferations such as Spitz, blue or deep penetrating nevi (in addition to many others), the designation 'melanocytic tumor of uncertain malignant potential' (MELTUMP) is our preferred term for such lesions, as it aptly captures the diagnostic and prognostic challenge they represent.^{2–8} The designation MELTUMP is a provisional diagnosis and one of exclusion; although one may favor a benign or malignant characterization, a definitive diagnosis is not always possible. As prefaced above, we acknowledge that the term MELTUMP is not universally used (and we

ask the reader to substitute their preferred alternate term if necessary). Irrespective of nomenclature, such lesions require expert consultation and prompt aggressive management suited for a possible diagnosis of melanoma.

As the genetic basis of melanocytic tumor biology is further understood, comparative genomic hybridization (CGH) has emerged as a novel tool to help distinguish the behavior of such difficult lesions by identifying chromosomal abnormalities associated with melanoma or the lack thereof in melanocytic nevi.⁹ However, the use of CGH to predict tumor behavior is inherently limited by its novelty, as long-term clinical follow up is lacking. We present a case of a lesion on the right cheek of a young boy that we believed was best defined as a MELTUMP, was found to lack chromosomal abnormalities by CGH and later was found to have associated sentinel lymph node metastasis. We then discuss the case and its implications in the approach to characterizing and managing these perplexing lesions.

Report of a case

A deeply pigmented lesion on the lateral right cheek of a 4-year-old boy had been present for 6 months. The patient's guardians did not notice any change in the lesion during the period of observation; the lesion was never pruritic, bleeding or painful. Removal by elliptical excision was completed. Microscopic sections showed a slightly wedge-shaped lesion with a dermal component of oval melanocytes with abundant cytoplasm and hyperchromatic nuclei and with an overlying ill-defined lentiginous epidermal component (Fig. 1). The dermal tumor cells extended along skin adnexal structures into the deep dermis without the evidence of maturation. Two mitotic figures were identified in one high-power ($\times 40$) field, including one mitotic figure at the base of the lesion (Fig. 2). There was a focally dense lymphocytic infiltrate within the lesion, and small foci suggestive of tumor necrosis were noted. In addition, a Ki-67 immunostain performed at the original institution revealed an increased proliferative index, with staining of clusters of cells in the lower part of the lesion.

The diagnosis rendered initially at another institution was atypical deep penetrating nevus, and the lesion was sent for consultation including high-resolution array CGH testing of the entire genome, which showed no genomic abnormalities associated with melanoma. A diagnosis of deep penetrating nevus was then favored. The lesion was later reviewed at our institution and was interpreted as a MELTUMP. Although features of a deep penetrating nevus were noted, there was concern for an unusual melanoma because of the presence of mitotic figures, areas suspicious for tumor necrosis and tumor infiltrating lymphocytes.

A subsequent sentinel lymph node biopsy of this patient revealed multiple small tumor deposits, approximately five in total, with sizes of the deposits ranging from 0.1 to 0.2 mm. The tumor cells were enlarged with abundant pigment and with moderately large, irregular nuclei and conspicuous nucleoli (Fig. 3). The lymph nodes were diagnosed at our institution as 'metastatic melanocytic tumor of uncertain malignant potential'.

Discussion

This case illustrates the difficulty in characterization of certain melanocytic tumors that defy conventional classification and what is understood regarding melanocytic tumorigenesis. This reported lesion has features of a deep penetrating nevus, but it also has certain malignant features such as mitotic activity, associated tumor infiltrating lymphocytes and areas suspicious for necrosis. An attempt to characterize lesions like these with certainty is virtually impossible, and diagnostic reproducibility is quite difficult, as seen in recent fora

where attempts were made to reach diagnostic consensus with respect to similar lesions.^{1,6} In a tutorial held at the XXIX Symposium of the International Society of Dermatopathology in Graz, Austria, Cerroni and colleagues looked at 57 atypical melanocytic lesions to assess both the diagnostic reproducibility of these lesions as well as the potential features that may help in the categorization of these tumors. Diagnostic consensus was found to be exceedingly rare, even among a group of international experts.⁶ Additionally, among the several histopathologic criteria examined in this exercise, only three were found statistically different in the two groups with favorable and unfavorable behavior based on clinical follow up: presence of mitoses, mitoses near the base and associated inflammatory infiltrate. Our lesion met all three of these criteria, which may correlate with the locoregional metastatic capacity that this proliferation later showed.

The lack of chromosomal abnormalities as assessed by CGH, with later regional lymph node metastasis found in the same patient, is a unique feature which has not been reported in the literature thus far. The CGH result and subsequent local tumor spread suggest genetic variance between these lesions and melanoma and are perhaps indicative of low malignant potential. Our case had approximately five small tumor deposits seen in a lymph node. The cytologic atypia found in these intraparenchymal deposits, which mirrors those found in the original lesion, bolstered somewhat by positive HMB-45 staining not typically seen in intranodal melanocytic nevi, supports the diagnosis of true locoregional tumor spread.^{10,11} CGH analysis performed on the original lesion, in this particular case potentially complicated by extensive lymphocytic tumor infiltration, revealed no genomic abnormalities associated with melanoma, which favored a benign characterization. The later development of locoregional metastasis does not suggest the fallibility or inadequacy of CGH testing, which impressively translates the genetic underpinnings of melanoma into functional patient testing. However, this relative genomic stability may suggest that these lesions represent a form of low-grade malignancy apart from conventional melanoma and could explain the incongruity of locoregional spread being a relatively common occurrence with the uncommon development of progressive disease. More comprehensive study is needed to validate this assertion.

We feel this case raises the distinct possibility that the histopathologic and behavioral ambiguities seen in this subset of difficult lesions may translate to ambiguous genetic profiles and suggest these tumors represent a biological entity apart from conventional melanoma and melanocytic nevi.

While sentinel lymph node biopsy was performed in this case, we believe that it represents a useful prognostic tool in the management of those with melanoma; the role of lymph node biopsy in MELTUMP has not yet been established. Recent studies have looked at concurrent tumor deposits in lymph nodes of atypical melanocytic lesions and show that these lesions rarely progress to overt malignancy. A study of atypical spitzoid tumors at one institution showed that roughly half of 67 cases contained tumor deposits in lymph nodes, while only one patient of the subset died of progressive disease.¹² Other studies have presented similar findings.^{13–21} It appears that lymph node involvement in association with tumors characterized as MELTUMP occurs frequently and the incidence of subsequent deadly disease is low. However, the documentation of spread to lymph nodes and the potential for progressive disease should not be taken lightly, and the lack of large studies with long-term follow up precludes the absolute dismissal of lymph node sampling. Therefore, we suggest that such nodal deposits be diagnosed as ‘metastatic melanocytic tumor of uncertain malignant potential’, a term that sufficiently reflects the biologic uncertainty that these nodal deposits pose. We prefer the use of the term ‘metastatic MELTUMP’, as it raises the distinct possibility that lymph node metastases in these lesions may represent a low-grade malignancy. Currently, it is unclear how the presence of multiple small (1–2 mm) tumor

deposits in a lymph node, as seen in our case, reflects tumor behavior, and the role of sentinel lymph node biopsy has not been proven to be a useful predictive tool in these lesions. However, the lack of prospective and comprehensive analysis should still warrant discussion with the patient and family regarding the possibility of sentinel lymph node sampling, which may prove to hold prognostic relevance with further study.

Finally, this case illustrates that attempts to categorize atypical melanocytic lesions as benign or malignant based on molecular testing alone may prove inaccurate and potentially dangerous. In this respect, histopathologic assessment remains the most important diagnostic arbiter. Once a lesion is found to be an atypical melanocytic proliferation based on histopathologic assessment, an open dialogue should be established between physician and patient that clarifies the inherent difficulty in predicting clinical behavior, which is an acknowledgement of the potentially unique biology of these lesions rather than an admission of diagnostic failure. We believe that histopathologic criteria such as dermal mitotic activity, inflammatory infiltration and the presence of nodal deposits can prove helpful in defining more aggressive tumors; however, none of these criteria can be interpreted as definitive. All cases must be evaluated individually, generally with complete surgical excision and close follow up recommended. Further study, including sentinel node evaluation, molecular analysis and long-term clinical follow up, is needed to definitively categorize these difficult lesions.

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Fig. 1.

A) Scanning magnification view of the wedge-shaped lesion showing a deep dermal melanocytic proliferation (2.5 $\times$). (B) Tumor-infiltrating lymphocytes are seen between large melanocytes with prominent nucleoli (20 $\times$). (C) A focus suggestive of tumor necrosis is present (40 $\times$).

Fig. 2.

Mitoses present at the base of a lesion (Left, black square, higher magnification in inset) and two in the same high power field (Right, black squares and insets). There is an inflammatory cell infiltrate in this lesion.

Fig. 3.

A) High power view of lymph node deposit shows cytologically atypical pigmented tumor cells that are similar to the original lesion, with (B) corresponding HMB45 immunostain positivity. (C and D). Other intraparenchymal deposits are also HMB45-positive.