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Proliferation indices correlate with diagnosis and metastasis in diagnostically challenging melanocytic tumors☆

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Summary The diagnosis of melanocytic lesions remains a formidable challenge in dermatopathology. For diagnostically challenging lesions, ancillary tests are available to inform the diagnosis, including immunohistochemistry and molecular testing (particularly fluorescence in situ hybridization [FISH]). However, the test result that most robustly informs the diagnosis remains controversial. Thirty-seven diagnostically challenging melanocytic lesions from our consultation service were reviewed. Histopathologic, immunohistochemical, and second-generation FISH results (NeoGenomics; probes 6p25, 8q24, 11q13, 9p21, and centromere 9) were correlated with the final consensus diagnosis and clinical follow-up using logistic regression and Fisher exact test. Based on histopathologic and immunohistochemical features, cases were designated as "favor benign" (n = 19) or "favor malignant" (n = 18) by a consensus group of up to 7 dermatopathologists. The sensitivity of FISH for the diagnosis of melanoma was 39%, and the specificity was 84%. Univariate logistic regression models for a final diagnosis of melanoma showed that only increased Ki-67–positive dermal tumor cells ($\geq 5\%$; $P = .01$) significantly correlated with the diagnosis of melanoma. FISH result did not correlate with the final diagnosis (melanoma or nevus; $P = .26$). Follow-up (range, 8-29 months) was available for 35 cases (19 diagnosed as nevus and 16 as melanoma), and metastases (restricted to sentinel lymph nodes) were detected from 5 melanomas (3 FISH negative and 2 FISH positive). Only increased dermal mitotic figures ($> 1/mm^2$) correlated with metastases to sentinel lymph nodes ($P = .04$). Thus, in the classification of diagnostically challenging melanocytic lesions, indices of proliferation emerge as the most informative diagnostic adjuncts—correlating with diagnosis and clinical behavior, respectively.

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1. Introduction

Melanoma is the most common among the fatal forms of skin cancer. Early stage melanoma carries an excellent prognosis with a 5-year survival rate of 98%, which declines to 63% with regional metastasis and 16% with distant metastasis [1]. Multiple studies have demonstrated an increasing incidence of melanoma over the past 50 years. Some authors have attributed this to environmental changes and excess ultraviolet light exposure [2], whereas others attribute this to increased screening and sampling of suspicious pigmented lesions [3].

Most melanocytic lesions can be reliably diagnosed as nevus versus melanoma on the basis of histopathologic features alone. For diagnostically challenging lesions, immunohistochemical studies provide additional refinement to light microscopy. Useful markers include those of melanocytic differentiation/maturation, such as HMB-45 [4], and markers of proliferation, including Ki-67 (MIB-1) [5]. However, a small subset of cases remains for which there is considerable interobserver variability in the diagnosis even among experts in dermatopathology [6]. These lesions comprise a spectrum of "diagnostically challenging melanocytic lesions" (DCMLs), and their incidence continues to rise.

One of the most important advances in the biology of melanocytic tumors was the application of comparative genomic hybridization (CGH) [7]. The earliest CGH studies demonstrated that ~96% of melanomas exhibited gains and losses in portions of chromosomes, whereas most melanocytic nevi typically lack abnormalities in chromosomal copy number [8]. This fundamental genomic disparity was then exploited diagnostically to differentiate malignant melanocytic tumors from benign ones. However, CGH has limitations of cost and in some cases technical feasibility; thus, fluorescence in situ hybridization (FISH) emerged as a surrogate for CGH to identify melanocytic proliferations carrying the chromosomal copy number aberrations most typical of melanoma [9]. The earliest study to assess FISH in the differentiation of melanoma from nevus demonstrated a sensitivity of 86.7% and a specificity of 95.4% [10], and this observation has been confirmed in most proof-of-principle studies among different melanoma subtypes [11–15]. However, an important limitation common to all of these studies is their reliance on unambiguous nevi and melanomas to demonstrate the utility of FISH as an ancillary diagnostic test. There is therefore a critical need to determine how FISH and other conventional histopathologic and immunophenotypic parameters correlate with the final diagnosis and clinical behavior of DCMLs. In the latter category, first-generation FISH testing revealed more modest utility: a median sensitivity of 49% (range, 43%-60%) and a median specificity of 84% (range, 33%-89%) [16–18]. No study has as of yet specifically interrogated the relative contribution of second-generation FISH testing to the diagnosis of DCML in comparison to conventional histopathologic and immunohistochemical parameters.

Given the evolution of FISH [19], there is a critical need to determine which histopathologic, immunophenotypic, and molecular (ie, FISH) features most significantly inform the consensus diagnosis of DCMLs and, more importantly, which of these features correlate with clinical behavior. Here, we report the relative utility of histopathologic, immunohistochemical, and second-generation FISH features for diagnosis and prediction of the clinical outcome in a series of 37 prospectively collected DCMLs.

2. Materials and methods

2.1. Case selection and review of records

We reviewed the clinical and pathologic features of 37 consecutive DCMLs selected for immunohistochemical and FISH analysis from January 2013 through December 2014 in the Section of Dermatopathology at The University of Texas MD Anderson Cancer Center. For each lesion in the series, immunohistochemistry and FISH were performed to further characterize a DCML.

In our practice, we classify melanocytic lesions as DCMLs when they have histologic changes suggestive of melanoma but insufficient to allow definitive classification as such. Such lesions typically exhibit some of the following histopathologic and/or immunophenotypic features: (1) asymmetric architecture (both the pattern of the melanocytic tumor and the associated stromal response); (2) pattern of growth (confluence in the epidermis or expansile in the dermis); (3) dermal inflammation and/or fibrosis; (4) upward pagetoid migration within the epidermis, particularly at the periphery; (5) severe cytologic atypia (including enlarged and irregular nuclear membranes and/or prominent nucleoli); (6) dermal mitotic figures (particularly deep forms); (7) abnormal dermal maturation pattern (absence of progressive diminution in cell size with dermal descent on light microscopy or progressive smooth diminution of HMB-45 expression with dermal descent on immunohistochemistry); and (8) an increased dermal proliferative rate (particularly toward deeper aspects of the dermal melanocytes [≥5% Ki-67–positive dermal melanocytes]).

For each lesion, a preliminary diagnostic impression was rendered after a dermatopathology consensus during which routine and immunohistochemically stained sections were reviewed by up to 7 dermatopathologists (V. G. P., M. T. T., C. A. T., J. L. C., D. I., P. P. A., and P. N.). Each lesion was assigned a preliminary diagnosis of "favor benign" or "favor malignant." The results of the FISH study were then considered in the context of the histopathologic, immunophenotypic, and clinical features, and a final consensus diagnosis of either melanoma or nevus with atypical features was rendered. When FISH results indicated melanoma but the consensus diagnosis favored benign or when FISH results indicated benign but consensus favored melanoma, the case was re-reviewed by up to 7 dermatopathologists. In our experience, the final diagnosis reflected the original consensus impression.