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WHAT'S NEW IN PATHOLOGY?

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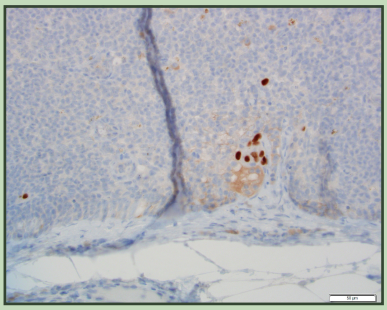
THE LATEST NEWS IN DERMATOPATHOLOGY

By Sara Shalin, M.D., Ph.D.

Sentinel lymph node evaluation in melanoma

Standard clinical practice is to perform a sentinel lymph node biopsy on melanomas with a Breslow depth > 1.0 mm and clinically negative regional lymph nodes. These sentinel lymph node biopsies are obtained by injecting a dye or radioactive tracer into the primary tumor bed. Radioactivity is detected in the regional lymph node basin, with the greatest activity corresponding to the "sentinel" node. Lymph nodes with > 10% of the greatest activity reading can also be considered a sentinel node, which is why several sentinel lymph nodes may be received.

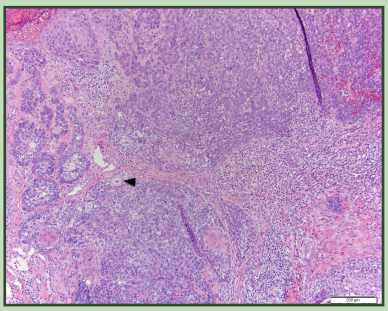


Micrometastases

The presence of metastatic melanoma in a sentinel lymph node generally prompts a completion lymphadenectomy, and by AJCC staging guidelines, even a single atypical melanocyte, detected by H&E or by convincing immunohistochemistry, qualifies as a positive lymph node. Thus, it is imperative that evaluation is comprehensive. While official guidelines have not been issued, most dermatopathologists recommend that the minimum evaluation of a sentinel lymph node biopsy (if negative for melanoma on initial sections) should include multiple deeper levels and multiple (generally at least two) immunohistochemical stains against melanocytic antigens. For a nice review, see Arch Pathol Lab Med 2013;137:1603.

Sebaceous neoplasia and testing for Muir-Torre Syndrome: the debate continues

Sebaceous neoplasia is associated with Muir-Torre Syndrome (MTS), a variant of Lynch syndrome. As sebaceous neoplasms (adenomas, sebaceomas and carcinomas) are relatively rare, their diagnosis should prompt consideration of screening for the syndrome. One screening method uses mismatch repair protein (MMR) immunohistochemistry (MLH1, MSH2, MSH6 and PMS2). Loss of staining indicates an absence of the MMR protein, which leads to microsatellite instability and tumor formation. Although MLH1 absence is most commonly detected in colorectal cancers of Lynch syndrome, MSH2 is the most frequently deleted MMR protein in sebaceous tumors. Up to 2/3 of sebaceous neoplasia will demonstrate loss of MMR proteins by immunohistochemistry (Hum Pathol 2016;49:1); however, the number of those patients ultimately determined to have a germline mutation (and MTS) is considerably smaller. Unlike colorectal carcinoma, where MMR IHC has high sensitivity (92% - 94%) and specificity (88% - 100%) in detecting Lynch syndrome, MMR IHC in sebaceous neoplasia has a reasonable sensitivity (85%) but low specificity (48%) (Genet Med 2014;16:711), leading to a high number of false positive screens.



Arrow: focal sebaceous differentiation

Lastly, a small subset of patients with MTS phenotype demonstrate microsatellite stable tumors and intact MMR protein staining due to different genetic mutations; these patients will have a false negative screen. Some authors advocate universal screening by MMR IHC for all sebaceous neoplasia. Others suggest offering ancillary testing to dermatologists, who can evaluate patients for other clinical criteria of the syndrome (selective screening). Concerns still exist regarding cost effectiveness of widespread screening and patient privacy and informed consent for what could be viewed as a surrogate for genetic testing (J Am Acad Dermatol 2016;75:1078).

Molecular testing in melanoma

Molecular testing has become a hot topic in dermatopathology. Both FISH and array CGH are relatively established molecular ancillary tests for melanoma; lesions harboring molecular aberrations are more likely to be malignant than those without. Currently, additional molecular based techniques are promoted as ancillary tests to help classify as malignant versus benign, to predict long term behavior of documented melanoma (indolent versus aggressive), and to predict response to targetable drug therapies.

MyPath® Melanoma:

A gene expression signature has been developed to help differentiate benign from malignant melanocytic neoplasms and is marketed by Myriad Genetic Laboratories as MyPath® Melanoma. This RT-PCR based assay is performed on formalin fixed, paraffin embedded tissue and evaluates expression levels of three groups of melanocytic related genes (PRAME involved in cell differentiation, S100A9 related genes involved in multiple cell signaling pathways, and immune related genes) and control / housekeeping genes for a total of 23 genes examined. Numeric scores are generated, with benign lesions scoring < -2 and malignant lesions classified as scores > 0. Scores between -2 and 0 are classified as indeterminate. Separate large cohorts have independently validated the gene expression signature using expert dermatopathologist diagnosis as the gold standard with sensitivities ranging from 90% - 91.5% and specificities ranging from 91% - 92.5% (J Cutan Pathol 2015;42:244; Cancer 2017;123:617). This assay may improve diagnostic confidence by better classifying lesions as benign or malignant; one study indicated that in a group of 218 diagnostically challenging lesions (80% were indeterminate by histiology; tumors were comprised mostly of atypical junctional melanocytic proliferations, dysplastic nevi and atypical Spitz tumors), the gene expression profile increased definitive diagnoses by 50% and reduced indeterminate diagnoses by 43%. This increase in diagnostic confidence also seemed to influence subsequent treatment recommendations (Medicine (Baltimore) 2016;95:e4887).

DecisionDx®-Melanoma:

This RT-PCR based assay, designed to provide prognostic information to patients diagnosed with primary cutaneous melanoma, is currently being marketed by Castle Biosciences, Inc. It is performed on formalin fixed, paraffin embedded tissue, and examines expression of 28 melanoma related genes and 3 housekeeping / control genes to stratify patients into two groups, class I (low risk) and class 2 (high risk). The gene expression profile was found to be an independent predictor of metastatic risk when developed and validated (Clin Cancer Res 2015;21:175). Moreover, when combined with sentinel lymph node biopsy results, one study found that the gene expression profile combined with sentinel lymph node biopsy improved prognostication. Sentinel lymph node negative patients with class 2 signatures had lower rates of disease free survival, distant metastasis free survival, and overall survival compared to sentinel lymph node negative patients with class 1 signatures (J Am Acad Dermatol 2015;72:780). Proponents of this assay say that the genetic signature provides additional prognostic information for patients and may help guide patient management (Curr Med Res Opin 2016;32:1599).

BRAF:

BRAF mutations are relatively common in cutaneous melanoma, leading to constitutive activation of the MAPK pathway. BRAF inhibitors (vemurafenib) may be used to treat metastatic or unresectable melanoma that demonstrates a BRAF mutation (most commonly V600E). BRAF mutation analysis is generally requested at the time of diagnosis of metastasis and can be performed with a variety of PCR based assays on paraffin embedded, formalin fixed tissue. An immunohistochemical stain (VE1) is available and seems to demonstrate good correlation with the molecular result, however it only detects the most common mutation (V600E) and not other variants.

PD-L1:

PD-L1 expression has been described in melanoma tumor cells and melanoma immune related cells. Although several different companion assays are on the market to assess for PD-L1 expression by immunohistochemistry (each linked to a different drug), there are currently no requirements for PD-L1 IHC testing in melanoma in order to treat with a PD-1 or PD-L1 inhibitor.

Conflict of interest statement: I have no financial relationships or conflicts of interest related to any of the assays discussed in this newsletter.

MEET THE AUTHOR

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Dr. Shalin has been a contributor and editorial board member of PathologyOutlines.com since 2014, publishing on topics ranging from melanoma biology to inflammatory skin disease.