# Histopathologic features of melanoma in difficult-to-diagnose lesions: A case-control study

Manuel Lora Gonzalez, MD,[a] Eric D. Young, BS,[b] James Bush, MD,[a] Katelyn McKenzie, BS,[c] Edgar Hunt, MD,[d] Viseslav Tonkovic-Capin, MD,[e] Melissa Jacobs, MD,[d] Michael Kucenic, MD,[f] and Garth R. Fraga, MD[a,g]
*Kansas City, Kansas; North Kansas City, Missouri; and Topeka, Kansas*

***Background:*** Dermatopathology is considered the gold standard for melanoma diagnosis, but a subset of cases is difficult to diagnose by histopathology.

***Objective:*** The goals of this study were to measure the accuracy of histopathologic features in difficult-to-diagnose melanocytic tumors and the interobserver agreement of those features.

***Methods:*** This is a case-control study of histopathologic features of melanoma in 100 difficult-to-diagnose melanocytic neoplasms (40 melanomas and 60 nevi). Slides were blindly evaluated by 5 dermatopathologists. Frequencies, predictive values, and interobserver agreement were calculated. Univariate and multivariate logistic regression analyses were performed to identify the most influential features in arriving at a diagnosis of melanoma.

***Results:*** Asymmetry, single-cell melanocytosis, solar elastosis, pagetoid melanocytosis, and broad surface diameter were most influential in arriving at a diagnosis of melanoma. Asymmetry and single-cell melanocytosis were most predictive of melanoma. Fleiss kappa was <0.6 for interobserver agreement in 9/10 histopathologic features of melanoma.

***Limitations:*** This study is limited by the small sample size, selection bias, and binary classification of melanocytic lesions.

***Conclusion:*** Our results indicate histopathologic features of melanoma in difficult-to-diagnose lesions vary in accuracy and reproducibility. (J Am Acad Dermatol 2017;77:543-8.)

***Key words:*** atypical nevus; diagnostic agreement; histopathology; melanoma.

Melanoma incidence in the United States is projected to rise over the next 15 years.[1] Dermatopathology is considered the gold standard for diagnosis of melanoma, but might be limited by interobserver disagreement.[2-7] Dermatopathology diagnosis is predicated upon

*Abbreviations used:*

| | |
|---|---|
| HFM: | histopathologic features associated with melanoma |
| ICD-9: | International Classification of Diseases, Ninth Revision |

From the Department of Pathology and Laboratory Medicine, Kansas University, Kansas City[a]; Department of Cancer Biology, Kansas University, Kansas City[b]; Department of Biostatistics, Kansas University, Kansas City[c]; MAWD Pathology Group, North Kansas City[d]; Department of Pathology, Veterans Affairs Medical Center, Kansas City[e]; Kansas Medical Clinic (Dermatology), Topeka[f]; and Department of Internal Medicine (Dermatology), Kansas University, Kansas City.[g]

Funding sources: None.
Conflicts of interest: None declared.
Poster presented at the American Society of Dermatopathology 53rd Annual Meeting, Chicago, Illinois, October 27, 2016.

Accepted for publication March 16, 2017.
Reprints not available from the authors.

Correspondence to: Garth R. Fraga, MD, University of Kansas Medical Center, Pathology and Laboratory Medicine, 3901 Rainbow Boulevard, Kansas City, KS 66160. E-mail: gfraga@kumc.edu.

Published online June 8, 2017.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.03.017

identification of histopathologic features associated with melanoma (HFM). Urso et al found substantial variance in sensitivity and specificity of 13 histologic criteria for melanoma in a study of 72 conventional melanomas and 73 conventional melanocytic nevi. They concluded that not all features hold the same diagnostic value.[8] A subset of melanocytic tumors is diagnostically challenging and considered difficult to diagnose.[9] Further investigation of HFM among these difficult to diagnose lesions is warranted to better understand their role in diagnostic discordance.[10]

**CAPSULE SUMMARY**

- There are limited data on the reliability of histopathologic criteria in difficult-to-diagnose melanocytic lesions.
- We found histopathologic features of melanoma in difficult cases vary in accuracy and reproducibility.
- These data could be used to build a diagnostic algorithm based upon the more influential histopathologic criteria for melanoma.

Prevalence of HFM has been studied in thin melanomas, melanomas that metastasized, and conventional nevi.[11-13] To calculate interobserver reproducibility and sensitivity and specificity of HFM, blinded studies including both benign and malignant lesions are necessary. Yet, these are relatively rare and have generally been limited to conventional nevi and melanomas. We undertook this study to evaluate HFM in the setting of difficult-to-diagnose melanocytic lesions. Understanding which HFM are most reproducible and influential in the diagnosis of melanoma could help in distinguishing melanoma from nevi in those with difficult-to-diagnose lesions.

In this study, 5 dermatopathologists independently examined 100 difficult-to-diagnose melanocytic tumors (40 melanomas and 60 melanocytic nevi) for 10 HFM. The study set consisted of melanocytic tumors, which were diagnostically indeterminate at the time of specimen receipt and had been referred for an expert consultation. We sought to obtain a more comprehensive assessment of HFM in difficult-to-diagnose cases by including both melanomas and melanocytic nevi in the study, blinding all participants to the expert diagnosis and requiring observers evaluate the tumors independently.

The goals of this study were to measure the frequency and predictive power of ten HFM in difficult-to-diagnose melanocytic lesions, determine which features had the most influence in classifying a case as benign or malignant, and calculate interobserver agreement in these features.

## METHODS

### Case selection

After approval from the Kansas University Institutional Review Board, we created a study set of 100 melanocytic neoplasms from a single community dermatopathology practice. The neoplasms were diagnostically indeterminate to the original dermatopathologist at the time of specimen receipt and had been referred for consultation to at least 1 of 2 nationally recognized dermatopathologists at an National Cancer Institute–designated melanoma center of excellence. Neoplasms were selected for inclusion if the expert dermatopathologist coded the lesion as a nevus (International Classification of Diseases Ninth Revision [ICD-9] 216) or as a melanoma (ICD-9 172.9). Neoplasms in which the expert coded the lesion as a neoplasm of uncertain behavior (ICD-9 238.2) were excluded from the study but tabulated to allow calculation of expert uncertainty. Neoplasms coded as melanomas were designated as cases and neoplasms coded as nevi were designated as controls. Neoplasms were retrospectively and sequentially selected until 100 benign and malignant expert diagnoses were identified. A single representative hematoxylin-eosin slide from each case was obtained to create a study set.

Ten histopathologic features of melanoma were selected for analysis: asymmetry, broad surface diameter, consumption of the epidermis, irregular nesting, single-cell melanocytosis (singly dispersed melanocytes predominate over nested melanocytes), pagetoid melanocytosis, absence of a vertical maturation gradient, solar elastosis, cellular atypia, and aberrant mitotic activity (atypical mitoses, peripheral mitoses, mitosis in a pagetoid melanocyte, or multiple mitoses). The criteria provided to the observers for documenting a feature as present or absent are listed in Supplemental Table I (available at http://www.jaad.org). Study set slides and standardized data entry sheets were distributed to 5 board-certified dermatopathologists from 4 different institutions. We required each observer to document each feature as present or absent and whether their final diagnosis was benign or malignant. All observers were blinded to the expert and fellow observers' final diagnoses. The majority observer diagnosis was defined as the favored diagnosis of 3 or more of the study participants.

Observers performed their analysis in their own institutions on their usual microscopes. They were not directed to focus on particular areas of the