3-22-2022

A Rare Case of Primary Cutaneous Signet-Ring Cell Melanoma With Discrepant Findings on Gene Expression Profiling and Chromosomal Microarray Analysis

Wyatt Boothby-Shoemaker

Michael Kwa
Henry Ford Health, mkwa1@hfhs.org

Laurie L. Kohen
Henry Ford Health, lkohen1@hfhs.org

Brandon M. Shaw
Henry Ford Health, bshaw1@hfhs.org

Ben J. Friedman
Henry Ford Health, bfriedm1@hfhs.org

Recommended Citation

Boothby-Shoemaker W, Kwa M, Kohen L, Shaw B, and Friedman BJ. A Rare Case of Primary Cutaneous Signet-Ring Cell Melanoma With Discrepant Findings on Gene Expression Profiling and Chromosomal Microarray Analysis. Am J Dermatopathol 2022.

A Rare Case of Primary Cutaneous Signet-Ring Cell Melanoma With Discrepant Findings on Gene Expression Profiling and Chromosomal Microarray Analysis

Wyatt Boothby-Shoemaker, BA, Michael Kwa, MD,† Laurie Kohen, MD,† Brandon Shaw, PhD,‡ and Ben J. Friedman, MD†‡*

Abstract: Melanoma with signet ring cell features is an exceptionally rare variant of primary cutaneous and metastatic melanoma. The molecular mechanisms underlying this unusual cytologic phenotype in malignant melanocytes are largely unknown. In this report, we aim to add to the literature by describing the histomorphological, immunophenotypic, gene expression, and cytogenetic findings in 1 recently encountered case.

Key Words: signet ring cell melanoma, gene expression profiling, microarray

(*Am J Dermatopathol* 2022;00:1–4)

INTRODUCTION

Melanoma with signet-ring cell features is an exceptionally rare, previously described histomorphologic variant of primary cutaneous and metastatic melanoma.[1–3] The molecular mechanisms underlying this unusual cytologic phenotype in malignant melanocytes is largely unknown. Because of the rarity of this phenomenon, there exists a significant potential for misdiagnosis by the unfamiliar pathologist. We recently encountered a melanocytic neoplasm in consultation that was consistent with signet-ring cell melanoma. Moreover, this lesion was initially misdiagnosed as a combined nevus in part because of a false-negative result obtained on a commercially available gene expression assay. In this report, we aim to add to the literature by describing the histomorphologic, immunophenotypic, and cytogenetic abnormalities of this unique tumor in detail. To our knowledge, this is the first detailed case study of this rare melanoma subtype that includes findings on both array comparative genomic hybridization (aCGH) and gene expression profiling (GEP).

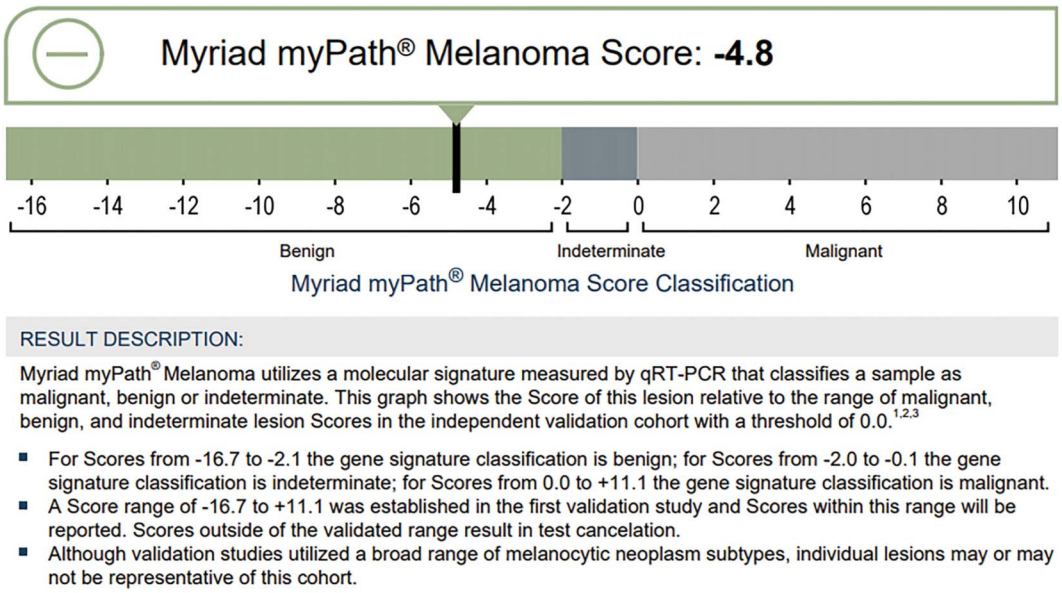

FIGURE 1. Commercially available gene expression assay report.

REPORT OF A CASE

A 43-year-old Caucasian man with paternal history of melanoma presented for a second opinion regarding a growing pigmented lesion on his back. A shave biopsy from the lesion had previously been interpreted as a "combined

From the *Michigan State University College of Medicine, Lansing, Michigan; and Departments of †Department of Dermatology, and ‡Department of Pathology & Laboratory Medicine, Henry Ford Health System, Detroit, MI.
The authors declare no conflicts of interest.
Correspondence: Ben J. Friedman, MD, Department of Dermatology, 3031 West Grand Blvd Suite 800, Detroit, MI 48202 (e-mail: Bfriedm1@hfhs.org).

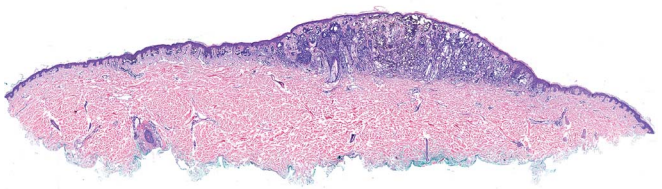

FIGURE 2. Histopathology. Scanning magnification demonstrating an asymmetric compound melanocytic proliferation (20×, original magnification).

compound nevus with features of epithelioid blue nevus." This diagnosis was notably rendered in the context of a "benign" score obtained on a commercially available, clinically validated 23-gene expression assay (Fig. 1).[4,5]

At scanning magnification, sections demonstrated a broad and asymmetric compound proliferation of melanocytes (Fig. 2). One half of the lesion consisted of a predominantly junctional component with largely nested melanocytes seen at the tips and sides of the rete pegs with bridging and papillary dermal fibroplasia. The other half contained a junctional component with similar qualities, in addition to a large dermal proliferation of melanocytes in variably sized expansile nests. Asymmetry was apparent and seen in both horizontal and vertical directions, and there was no conspicuous maturation evident (Fig. 3). On higher power, most melanocytes contained peculiar cytoplasmic vacuolization with eccentrically compressed and indented nuclei reminiscent of signet rings and lipoblasts, an uncommon finding in melanocytic nevi (Fig. 4). Nuclear pleomorphism was notably mild-to-moderate throughout much of the lesion.

Features worrisome for melanoma included the apparent asymmetry, uneven cytoplasmic melanization, the presence of large expansile nests in the dermis, lack of maturation, elevated Ki67 index (10%–15%), and disproportionate HMB45 reactivity in the deeper portions of the lesion (Fig. 5). Given the discrepant "benign" gene expression score, peculiar cytology, and deceptively low-grade nuclear pleomorphism, additional analysis via chromosomal microarray (via previously described methods[6]) was pursued. Multiple deleterious segmental gains and losses were detected, which was more indicative of a malignant phenotype and consistent with our impression of a malignant lesion based on the overall histomorphologic and immunophenotypic features.[7,8] Specifically, there were copy number gains in the 5p, 16p, 17p, and 20q regions; copy number losses in the 5p, 5q, 17p, and 20p regions; copy neutral loss of heterozygosity (LOH) were found in regions 5p, 5q, 16p, and 20p (Fig. 6).

DISCUSSION

Melanoma has been known to demonstrate unusual morphologies including rhabdoid, nevoid, balloon cell, sebocyte-like, desmoplastic, and dedifferentiated forms.[9] These morphologies may on occasions pose diagnostic difficulty in distinguishing between benign nevi and other nonmelanocytic malignant tumors. Signet ring cytology in melanoma is an exceedingly uncommon finding,[1,10] and may be

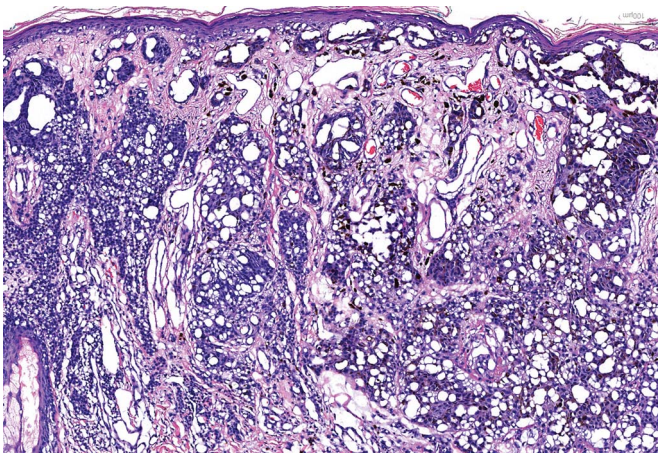

FIGURE 3. Histopathology. Medium power view demonstrating variably sized nests of melanocytes with patchy melanization and no conspicuous maturation in the dermis (100×, original magnification).

precipitated by the accumulation of substances within the cytoplasm that then compress the nucleus against the plasma membrane. Signet ring cells are perhaps most commonly associated with gastrointestinal adenocarcinomas, in which the cytoplasm fills with mucin. Although generally uncommon in cutaneous neoplasms, this phenomenon has rarely been reported in melanoma, squamous cell carcinoma, hidradenoma, cylindroma, basal cell carcinomas, mycosis fungoides, and liposarcoma. Bastian et al[1] proposed that the appearance of signet ring cells in a selection of primary and secondary cutaneous tumors resulted from the accumulation of a variety of intracytoplasmic material, including mucin, glycogen, vimentin, and keratin. Kocovski et al hypothesized that intracytoplasmic inclusions in signet ring cell melanoma were likely caused by vimentin based on immunohistochemical staining of 23 prior cases and findings of vimentin filaments on electron microscopy.[11] Whether these changes are analogous to and/or on the spectrum of the balloon cell and sebocyte-like cytology seen in other melanocytic lesions remains to be determined.[12]

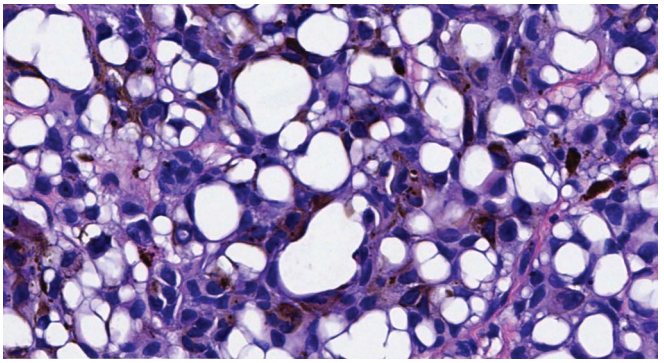

FIGURE 4. Histopathology. High-power view demonstrating numerous vacuolated melanocytes resembling signet ring-cells and lipoblasts (200x, original magnification).

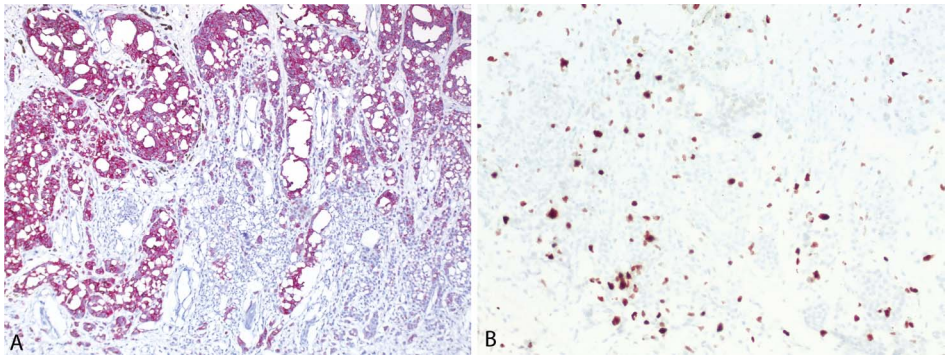

FIGURE 5. A, HMB45 immunohistochemical stain demonstrating uneven labeling with no gradient (100×, original magnification). B, MIB immunohistochemical stain demonstrating an elevated proliferation index (200×, original magnification).

To our knowledge, this is the first reported case of signet ring cell melanoma evaluated via aCGH. LOH in our case was identified on 5p, 5q, 16p, and 20p. These regions did not overlap with the 7 most frequent chromosomal arms demonstrating LOH in melanoma based on one study of 76 melanoma lines. This could perhaps implicate a unique cytogenetic signature for melanoma with signet-ring features, although larger studies focusing on this specific entity would be needed for confirmation.[13] Interestingly gains in 20q were among the most frequent cytogenomic findings in melanoma in that study, which provides further support for the diagnosis in this case.

Commercially available GEP assays are increasingly being used by dermatopathologists when faced with difficult melanocytic lesions to help support or refute a histomorphologic diagnosis of melanoma.[14] These often use quantitative reverse transcription polymerase chain reactions to measure the expression of multiple genes and assign a score to a lesion

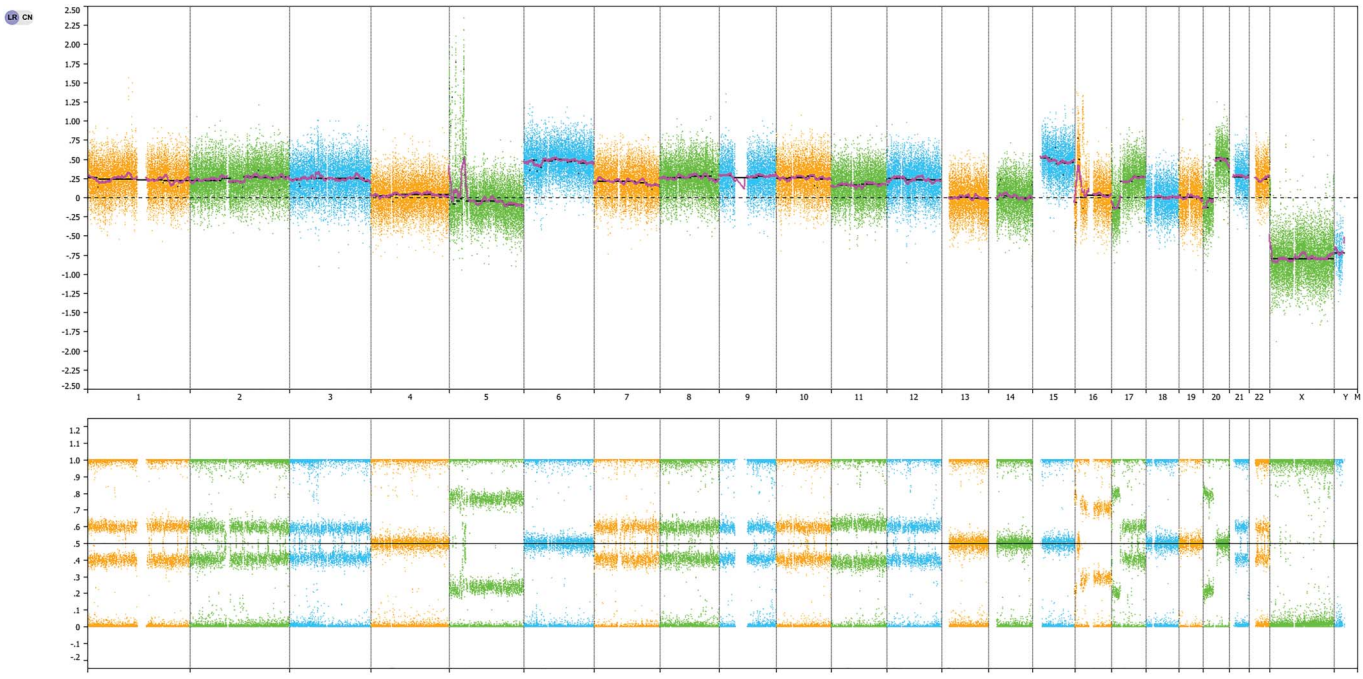

FIGURE 6. Chromosomal SNP array (upper panel: copy number data, lower panel: allelic ratio plot).

based on a proprietary, clinically validated algorithm. Based on the score, lesions are classified as "benign," "indeterminate," or "malignant." The test reports a sensitivity of 90%–94% and specificity of 91%–96% in establishing a diagnosis of malignant melanoma based on prior validation studies.[4] As demonstrated in this case, caution must be exercised when interpreting the results of GEP assays, especially in the setting of unusual histomorphologic variants that may have not been adequately represented in the initial validation assays. Moreover, validation of these tests has typically been based on consensus agreement with 2 or 3 expert dermatopathologists rather than clinical outcome. Studies to date that have compared the results of FISH, GEP, aCGH on the same cases, have generally found that aCGH tends to agree more with expert consensus diagnosis based on histopathology alone.[15] Given these limitations, adjunctive GEP for the diagnosis of melanoma is still not fully endorsed by the American Society of Dermatopathology Acceptable Use Criteria, as more long-term outcome data are needed.[16]

REFERENCES

1. Bastian BC, Kutzner H, Yen Ts, et al. Signet-ring cell formation in cutaneous neoplasms. *J Am Acad Dermatol.* 1999;41:606–613.
2. Sheibani K, Battifora H. Signet-ring cell melanoma. A rare morphologic variant of malignant melanoma. *Am J Surg Pathol.* 1988;12:28–34.
3. Eckert F, Baricević B, Landthaler M, et al. Metastatic signet-ring cell melanoma in a patient with an unknown primary tumor. Histologic, immunohistochemical, and ultrastructural findings. *J Am Acad Dermatol.* 1992;26:870–875.
4. Clarke LE, Flake DD, Busam K, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. *Cancer*. 2017;123:617–628.
5. Clarke LE, Warf MB, Flake DD, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. *J Cutan Pathol.* 2015;42:244–252.
6. Friedman BJ, Hernandez S, Fidai C, et al. A pediatric case of pigmented epithelioid melanocytoma with chromosomal copy number alterations in 15q and 17q and a novel NTRK3-SCAPER gene fusion. *J Cutan Pathol.* 2020;47:70–75.
7. North JP, Vemula SS, Bastian BC. Chromosomal copy number analysis in melanoma diagnostics. In: *Molecular Diagnostics for Melanoma*. Totowa, NJ: Springer; 2014:199–226.
8. Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. *Dermatol Ther.* 2006;19:40–49.
9. Cota C, Saggini A, Lora V, et al. Uncommon histopathological variants of malignant melanoma: part 1. *Am J Dermatopathol.* 2019;41:243–263.
10. Kacerovska D, Sokol L, Michal M, et al. Primary cutaneous signet-ring cell melanoma with pseudoglandular features, spindle cells and oncocytoid changes. *Am J Dermatopathol.* 2009;31:81–83.
11. Kocovski L, Alowami S. Signet-ring cell melanoma: a potential diagnostic pitfall. *Am J Dermatopathol.* 2014;36:985–988.
12. Kazlouskaya V, Guo Y, Maia-Cohen S, et al. Clear-cell melanocytic lesions with balloon-cell and sebocyte-like melanocytes: a unifying concept. *Am J Dermatopathol.* 2014;36:380–386.
13. Stark M, Hayward N. Genome-wide loss of heterozygosity and copy number analysis in melanoma using high-density single-nucleotide polymorphism arrays. *Cancer Res.* 2007;67:2632–2642.
14. Emanuel PO, Andea AA, Vidal CI, et al. Evidence behind the use of molecular tests in melanocytic lesions and practice patterns of these tests by dermatopathologists. *J Cutan Pathol.* 2018;45:839–846.
15. Reimann JDR, Salim S, Velazquez EF, et al. Comparison of melanoma gene expression score with histopathology, fluorescence in situ hybridization, and SNP array for the classification of melanocytic neoplasms. *Mod Pathol.* 2018;31:1733–1743.
16. Fung M, Vidal C, Armbrecht E, et al. Appropriate use Criteria (AUC) for ancillary diagnostic testing in dermatopathology: new recommendations for 11 tests and 220 clinical scenarios from the American society of Dermatopathology AUC committee. *J Cutan Pathol.* 2021;49:231–245.