Received: 26 September 2021 | Revised: 17 May 2022 | Accepted: 19 May 2022

DOI: 10.1111/cup.14263

CASE STUDY

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Fatal melanoma with a novel *MYO5A-BRAF* fusion and small associated conventional nevus: A case report and review of literature

Hannah E. Clark BS[1] | Yuan Yu Michael Huang MD[2] | Gail H. Vance MD[3,4] | Ahmed K. Alomari MD[2,3]

[1]Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Dermatology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[3]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

[4]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence
Ahmed K. Alomari, MD, Indiana University School of Medicine, Indianapolis, IN 46202, USA.
Email: akalomar@iu.edu

Abstract

Kinase fusions play an important role in the pathogenesis of Spitz neoplasms and occasionally non-Spitz neoplasms. We report a case of a 19-year-old woman with a growing nodule on the scalp, morphologically consistent with a diagnosis of melanoma with epithelioid features arising in association with small nevus. This tumor aggressively metastasized and failed to respond to immunotherapy. Next-generation sequencing of a metastatic focus revealed an *MYO5A-BRAF* kinase fusion with a low mutational burden and fluorescence in situ hybridization (FISH) of the primary melanoma showed similar results. FISH testing of the associated nevus failed because of technical reasons. *MYO5A* has rarely been reported as the fusion partner with *BRAF*-rearranged melanocytic tumors. Moreover, this case raises speculations and contributes to the growing literature on the pathogenesis, nomenclature, and tumorigenic pathways in kinase-fusion melanomas. The patient succumbed to disease, which is in concordance with some literature suggesting aggressive behavior of *BRAF* fusion melanomas with *TERT* promoter mutations.

KEYWORDS
genomic analysis, kinase-fusion mutation, Spitz melanoma, spitzoid neoplasm, *TERT*-promoter mutation

1 | INTRODUCTION

BRAF fusions have been identified as the oncogenic driver of a small (4%–8%) subset of Spitz neoplasms.[1–5] Histopathologically and clinically, these neoplasms tend to cluster in the atypical Spitz tumor and Spitz melanoma categories.[5] Several fusion partners have been previously identified; however, *MYO5A* has only been reported in a single atypical Spitz tumor with indolent biologic behavior.[6] In non-Spitz neoplasms, *BRAF* fusions have rarely been reported in mucosal and cutaneous acral melanomas.[7,8] There are also few reports of giant congenital nevi harboring *BRAF* fusions.[9]

In this report, we describe the clinical, histopathologic, and molecular characteristics of a fatal melanoma with epithelioid cytomorphology, an *MYO5A-BRAF* fusion and small nevus remnants. We also discuss the potential contribution of these findings into the evolving understanding and classification of similar neoplasms, including their possible evolution from precursor lesions.

2 | CASE REPORT

A 19-year-old woman without notable medical history presented with a 2.0-cm growing, increasingly pruritic cobblestoned nodule of the left parietal scalp of unknown duration. An excisional biopsy specimen showed an expansile polypoid compound melanocytic proliferation with sheets of large epithelioid cells lacking maturation and showing a mitotic rate of 3 mitotic figures/mm^2 in the dermis (Figure 1). HMB45 showed patchy weak staining in the dermal component, and Ki-67 highlighted a proliferation index of approximately 5% superficially.

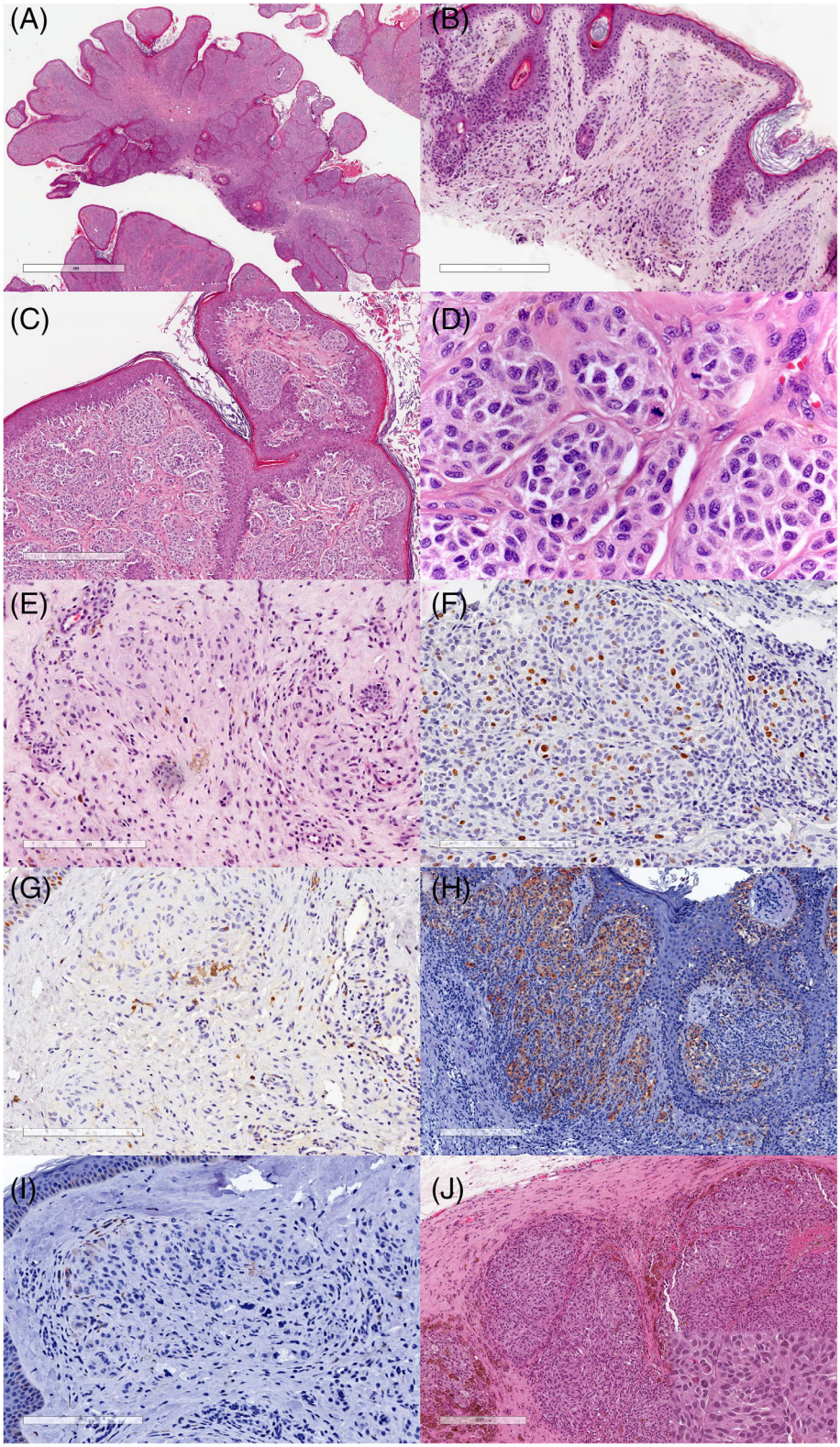

FIGURE 1 (A) The initial biopsy specimen showed multiple fragments of a polypoid melanocytic proliferation with sheet-like growth pattern (H&E). (B) One tissue fragment harbored background dermal nevus in close association with melanoma cells (upper left) (H&E). (C) Medium-power view of the melanoma (H&E). (D) Scattered dermal mitotic figures were present (H&E, ×600). (E) High-power view of the nevus component showing conventional morphology (H&E). (F) High Ki-67 index in the melanoma component. (G) Low Ki-67 index in the nevus component. (H) Patchy HMB45 staining in the melanoma component. (I) No HMB45 staining in the nevus component. (J) Medium-power view of a subcutaneous metastasis (inset: high-power view showing a mitotically active neoplasm) (H&E)

Four-probe melanoma fluorescence in situ hybridization (FISH) testing was positive for decreased *MYB*:*CEN6* ratio. These findings were consistent with a diagnosis of melanoma with epithelioid features and a Breslow depth of 3.8 mm. Importantly, one section showed clusters of nevic melanocytes consistent with nevus remnant (Figure 1). Subsequently, the patient underwent two surgical excisions, the latter of which was negative for residual tumor. No sentinel lymph node biopsy was performed. Four years later, the patient presented with widely metastatic disease involving her skin, brain, heart, and retroperitoneum. Targeted testing for *BRAF* V600E mutation from a cutaneous metastasis was negative (Figure 1), and the patient received multiple rounds of immunotherapy including single-agent nivolumab and ipilimumab followed by combination therapy. Despite the therapeutic intervention, the patient's disease slowly continued to progress and a biopsy of a metastatic focus from the right adrenal gland was performed and studied further.

Genomic analysis of the adrenal metastatic tissue (FoundationOne CDX) revealed a novel in-frame fusion between exon 35 of *MYO5A* (one of myosin V heavy-chain genes) and exon 9 of *BRAF*, which probably represents the oncogenic driver mutation. Additionally, the study showed a hotspot *TERT*-promoter mutation and an overall low tumor mutation burden (TMB) at 1 mutation per megabase (Muts/Mb). A pathogenic point mutation of *CDKN2A* was also present. Table 1 summarizes the detailed genomic findings of the metastatic focus from the adrenal gland. To confirm the biologic relationship to the patient's primary melanoma of the scalp, FISH utilizing a dual-color, break-apart *BRAF* FISH probe was performed on a paraffin-embedded tissue section from the left anterior parietal scalp. Two hundred cells were analyzed by fluorescent microscopy. One hundred sixty-nine (84.5%) cells showed rearrangement of *BRAF* with one to two fusions (unrearranged pattern) per cell and one to two 3′ signals, indicating rearrangement and loss of the 5′ signal possibly because of the translocation (Figure 2). Because of poor signal quality, evaluation of the presence of *BRAF* rearrangement in the small tissue fragment with nevus could not be achieved. The patient was scheduled to receive trametinib; however, she was unable to receive trametinib because of worsening hepatic function and died 4 months following genomic testing.

TABLE 1 Tumor precision genomic analysis biomarkers and genomic alterations found with precision genomic analysis

Biomarker findings		
Microsatellite status	Stable	
Tumor mutational burden	1 Muts/Mb	
Genomic findings		
BRAF	MYO5A-BRAF (M35: B9) fusion	Likely driver
PTEN	Splice site 635-1G>T	Pathogenic (score 0.99)
APC	T1556fs*3	Unknown significance
CDKN2A/B	p16INK4a P81L	Pathogenic (score 0.98)
DNMT3A	AP804S	Pathogenic (score 0.99)
TERT promoter	−146C>T	Hotspot mutation

Note: Analysis performed by FoundationOne CDx.

3 | DISCUSSION

The most recent (fourth) edition World Health Organization (WHO) classification of skin tumors defines Spitz melanocytic neoplasms based on a combination of morphologic and molecular characteristics.[10] In 4%–8% of these tumors, the driver molecular event is a chromosomal-rearrangement-induced fusion involving the *BRAF*

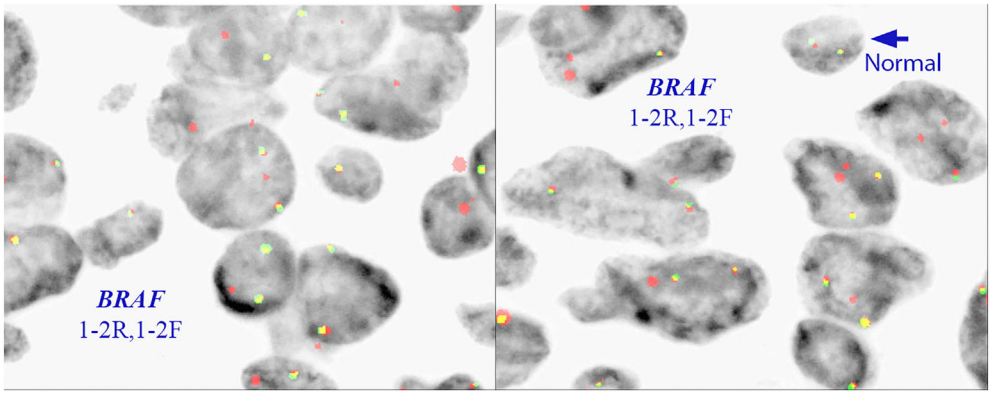

FIGURE 2 *BRAF* analysis of the primary tumor by fluorescence in situ hybridization (Zytovision *BRAF* breakapart probe). A yellow signal (orange and green fused) indicates intact *BRAF* without rearrangement, on the other hand, green or red/orange signals indicate rearrangement occurring at the loci identified by the probes. There are one to two fusions (unrearranged pattern) per cell and one to two 3′ (red/orange) signals, indicating rearrangement and loss of the 5′ signal possibly because of the *MYO5A*/*BRAF* translocation. The direct-labeled orange fluorochrome probe hybridizes proximal, and the direct-labeled green fluorochrome probe hybridizes distal to the *BRAF* gene breakpoint region.

gene.[4,5] Several fusion partners have been reported in the literature including, but not limited to, *MAD1L1*, *AGK*, *TRIM24*, *DYNC1I2*, *AKAP9*, *ZKSCAN1*, *AGK*, *MZT1*, *CUX1*, and *SLC12A7*.[2] On the other hand, *MYO5A* has been reported as a fusion partner in Spitz tumors with *RET*, *NTRK3*, and *ROS1* fusions.[2] To the best of our knowledge, an *MYO5A-BRAF* kinase fusion has been reported in a single atypical Spitz tumor with indolent behavior.[6]

In melanocytic neoplasia, *BRAF* fusions are not limited to the Spitz category. They have been rarely identified in acral, superficial spreading, and mucosal melanomas as well as in benign giant congenital nevi.[7,8] Further, a case of *PRKAR1A*-inactivated melanoma with background giant congenital nevus, in-frame *FAM39B-BRAF* gene fusion, and no spitzoid features is noted.[11]

In this patient, accurate classification and nomenclature might be a challenge as the morphology is not supportive of an undisputable diagnosis of Spitz lineage. Moreover, the presence of conventional background nevus, although its association with melanoma is not definitive, argues against Spitz lineage. On the other hand, the few previously reported cases of non-Spitz *BRAF* fusion melanomas represent a diverse group of mucosal melanomas, acral melanomas, superficial spreading melanomas, and melanomas arising within giant congenital nevus, none of which represents an appropriate designation of the melanoma in this patient.[7,8,11]

Progression from precursor Spitz nevi is infrequently reported in melanomas with *BRAF* fusion; however, it is believed to represent the major underpinning for their pathogenesis according to the WHO's evolutionary pathways for melanoma development.[10,12] Our current example of *BRAF*-rearranged melanoma arose in close association with a small nevus with conventional morphology; however, because of technical failure, we could not document the presence of *BRAF* rearrangement in the nevus component. Based on these findings, one could only speculate an alternative pathway of *BRAF*-kinase fusion melanoma development from small precursor lesions with non-spitzoid morphology, similar to that rarely reported in giant congenital nevi. Moreover, one could also postulate that the *BRAF* fusion represents a secondary event that initiated the growth of the melanoma but not the precursor nevus. Finally, it is also feasible that the two components are biologically unrelated. More studies are clearly needed to better characterize similar neoplasms to provide informed data on their classification, behavior, and prognosis.

A *TERT*-promoter mutation is also found in our case. This mutation is well documented in aggressive cutaneous conventional melanoma.[13] However, there are limited data on its role in *BRAF*-rearranged melanomas. In a cohort of 56 individuals with spitzoid neoplasms, four tumors had *BRAF* fusion and were morphologically consistent with melanoma; however, only one had a *TERT*-promoter mutation and that patient died from disseminated disease.[13]

Notably, the melanoma described in our case has a low TMB, similar to other kinase fusion melanomas in the literature.[4,5] In contrast, conventional melanomas typically have high TMB.[14] Previous reports have suggested higher TMB may be associated with greater response to immunotherapies, including longer progression-free survival and overall survival.[15,16] The low TMB in our patient may be the reason for her lack of response to immunotherapies and argues for triaging cases for molecular profiling early in the disease course if a kinase-fusion pathogenesis is suspected.

Perhaps the most important clinical implication of identifying and understanding these driver mutations lies with the potential to use targeted therapy for aggressive neoplasms.[17] Multikinase inhibitors have activity against *BRAF*, and data suggest *BRAF*-activating mutations or fusions may confer sensitivity to multikinase inhibitors such as sorafenib and regorafenib.[18] Inhibitors of MEK and ERK, fellow members of the MAPK pathway, may also be viable treatment options of *BRAF*-activating alterations.[18] Unfortunately, our patient succumbed to her disease before more targeted therapy could be utilized.

In conclusion, we describe a case of fatal melanoma with a novel *MYO5A-BRAF* kinase fusion. We raise, although we could not confirm, malignant transformation within small non-spitzoid nevi as a potential pathway for *BRAF* fusion melanoma development, a phenomenon that we believe warrants further investigation. The aggressive behavior of our case is similar to few previously reported *BRAF* fusion tumors with *TERT*-promoter mutations, although this association requires confirmation by larger studies. Much diagnostic uncertainty remains in the field of kinase-fusion neoplasms, and our case contributes to the growing histopathological, genomic, and clinical characteristics of such an intriguing group of neoplasms.

ACKNOWLEDGMENTS

The authors would like to thank Ryan Stohler from the Department of Medical and Molecular Genetics at Indiana University School of Medicine for his assistance in fluorescence in situ hybridization analysis.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

ORCID

Hannah E. Clark https://orcid.org/0000-0002-9256-0245
Ahmed K. Alomari https://orcid.org/0000-0002-3776-5053

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How to cite this article: Clark HE, Huang YYM, Vance GH, Alomari AK. Fatal melanoma with a novel *MYO5A-BRAF* fusion and small associated conventional nevus: A case report and review of literature. *J Cutan Pathol*. 2022;49(9):808-812. doi:10.1111/cup.14263