Case Presentation

Blue nevus–like melanoma: A rare entity

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Abstract

A 34-year-old man from Guinea-Bissau presented with a rapidly growing tumor on his right foot over 6 months, arising from a long-standing pigmented papule present for more than 20 years. Clinical examination revealed an exophytic black tumor with ipsilateral inguinal lymphadenopathy. Histopathological analysis showed an epithelioid and fusiform melanocytic proliferation in the dermis with abundant melanin. Immunohistochemical staining demonstrated diffuse positivity for Sox-10, Melan-A, HMB45, and PRAME. A diagnosis of blue nevus–like melanoma (BNM) was confirmed. BRAF V600 mutation testing on a cutaneous metastasis was negative. Staging imaging revealed widespread metastases involving lymph nodes, brain, lungs, liver, stomach, duodenum, colon, adrenal glands, pancreas, gallbladder, and bones. Despite 4 cycles of ipilimumab/nivolumab immunotherapy, the disease progressed, and the patient died 4 months after diagnosis. BNM is a rare melanoma variant, often arising from a pre-existing blue nevus, with aggressive potential and frequent lymph node metastasis. The molecular heterogeneity of BNM and the limited therapeutic options underscore the need for further research into targeted therapies and prognostic biomarkers for this rare melanoma subtype.

Introduction

The term *blue nevus–like melanoma* (BNM) refers to a heterogeneous group of melanomas that either arise in association with common or cellular blue nevi or develop de novo but architecturally or cytologically mimic cellular blue nevus.[1] Owing to its rarity, diagnosing BNM can be challenging and requires correlation between clinical and histopathological findings. We describe a young patient with metastatic BNM, highlighting the therapeutic challenges associated with this rare entity.

Case Synopsis

A 34-year-old man from Guinea-Bissau, with no significant medical history, presented to the emergency room with a rapidly growing tumor on his right foot over the previous 6 months. He reported a long-standing pigmented papule present for more than 20 years. Clinical examination revealed an exophytic black tumor measuring 10 × 8 × 6 cm, accompanied by satellite lesions (**Figure 1**). A large mass was also detected in the ipsilateral inguinal region, consistent with lymphadenopathy.

An incisional biopsy was performed, and histopathological examination revealed a pleomorphic epithelioid and fusiform melanocytic proliferation in the dermis with abundant melanin, sparing the epidermis (**Figure 2** and **Figure 3**). Immunohistochemical staining showed diffuse positivity for Sox-10, Melan-A, HMB45, and PRAME (**Figure 4**), confirming the diagnosis of BNM. Immunostaining for BAP1 demonstrated retained nuclear expression. BRAF V600 mutation testing on a cutaneous metastasis was negative, and owing to institutional limitations, NRAS testing was not performed.

Staging imaging revealed extensive metastatic dissemination to the lymph nodes, brain, lungs, liver, stomach, duodenum, colon, adrenal glands, pancreas, gallbladder, and bones. The patient began immunotherapy with ipilimumab and nivolumab. Despite completing 4 treatment cycles, the disease continued to progress, resulting in the patient's death 4 months after diagnosis.

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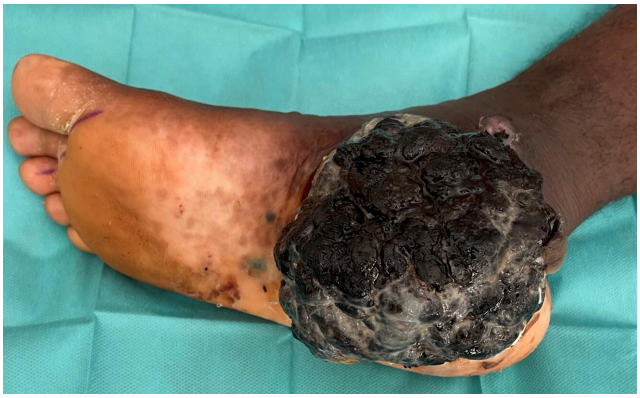

Figure 1. *Clinical presentation revealed exophytic black tumor with hyperpigmented satellite papules on the right foot.*

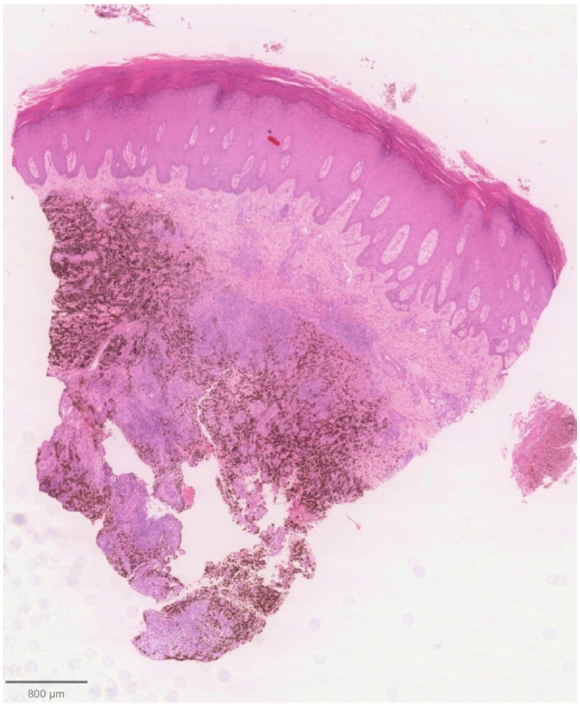

Figure 2. *Histopathologic features showing a dense aggregation of cells with intense melanin pigment in the mid and deep dermis, sparing the epidermis (hematoxylin-eosin, original magnification ×25).*

Case Discussion

The term *malignant blue nevus* was first introduced by Allen[2] to describe melanomas exhibiting histological features resembling a blue nevus. Since then, several authors have applied the term to describe a spectrum of entities, including malignant transformation of a pre-existing blue nevus, melanoma arising at the site of a previously excised blue nevus, melanoma with blue nevus–like histological features, or melanoma containing an admixed benign blue nevus component.[3] To improve diagnostic clarity, the term *BNM* has been proposed to encompass these lesions.[4]

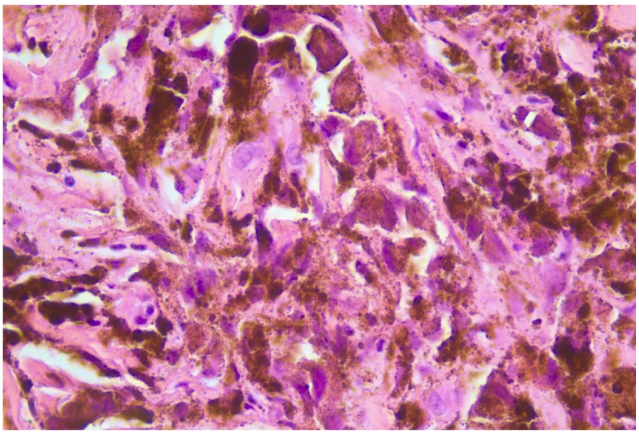

Figure 3. *Histopathologic features showing epithelioid and spindle cells with pleomorphic nuclei, dispersed chromatin, and prominent nucleoli (hematoxylin-eosin, original magnification ×400).*

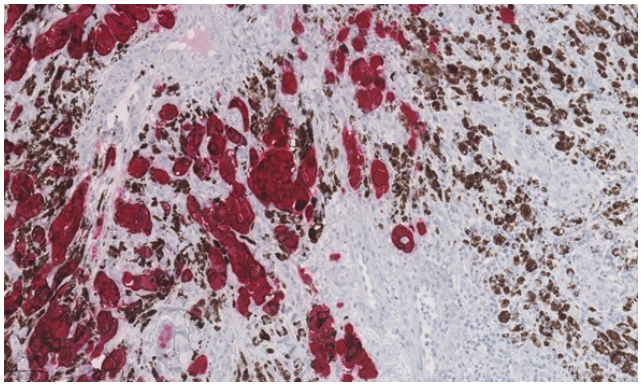

Figure 4. *Strong and diffuse nuclear positivity (red) in atypical melanocytes (PRAME immunohistochemistry [red chromogen] ×200).*

BNM is a rare melanoma variant that typically arises within a background of cellular blue nevus.[3] In rare instances, it may develop de novo without an identifiable benign precursor.[5] It occurs more commonly in men, usually in the fourth decade of life, and is most frequently located on the head and neck, although it may arise at any anatomical site.[3,6,7] Clinically, BNM is characterized by rapid enlargement, ulceration, and color changes, with lesions potentially reaching substantial sizes, ranging from 3 to 13 cm.[5] However, the histological criteria for diagnosing BNM remain poorly defined.[4]

The differential diagnosis includes cellular blue nevus, pigmented epithelioid melanocytoma (PEM) (formerly animal-type melanoma), and cutaneous melanoma metastasis.[5,7] Correlation with clinical features is essential for accurate diagnosis.[3] Histopathological features that help distinguish BNM from benign blue nevi include cytological atypia, such as nuclear pleomorphism, prominent eosinophilic nucleoli, and atypical mitotic figures, as well as widespread necrosis, often accompanied by palisading of tumor cells around necrotic areas.[4,5] BNM also

Table 1. *Comparison of Molecular and Histological Features in BNM and PEM.*

Feature	BNM	PEM
Common mutations	*GNAQ*, *GNA11*	*PRKAR1A* mutations, *PRKCA* fusions
BAP1 expression	Often lost	Usually retained
SF3B1 mutations	Present in subset	Rare
PRKAR1A/*PRKCA* alterations	Absent	Present
Histological features	Dermal proliferation of pigmented melanocytes with marked cytologic atypia, pleomorphism, large nuclei, prominent nucleoli; necrosis may be present	Heavily pigmented epithelioid and spindle cells with mild to moderate atypia and often bland nuclei; necrosis typically absent
PRAME expression	Frequently diffusely positive	Typically negative or only focal

Abbreviations: BNM, blue nevus–like melanoma; PEM, pigmented epithelioid melanocytoma.

frequently extends into the subcutis, and a junctional component is typically absent.[5]

Although common acquired nevi and melanomas often harbor BRAF or NRAS mutations, blue nevi and BNM characteristically carry *GNAQ* or *GNA11* mutations, similar to uveal melanoma.[6,7] These genes encode G-protein subunits, and their mutations activate the downstream MAPK pathway, promoting melanocytic proliferation.[7] BNM frequently contains additional mutations, such as in *BAP1* and *SF3B1*, which have been associated with malignant transformation. The co-occurrence of these mutations supports a multistep progression model from benign to malignant melanocytic lesions.[8] PEM, in contrast, often harbors *PRKAR1A* mutations or *PRKCA* fusions, distinguishing it from BNM and other melanoma subtypes.[9] Understanding these molecular differences is essential for accurate diagnosis and may guide future therapeutic strategies (**Table 1**).

In the present case, strong and diffuse PRAME expression, marked cytological atypia, the absence of a characteristic biphasic histologic pattern, and the rapid clinical progression with distant metastasis supported the exclusion of PEM and favored the diagnosis of BNM.

Several studies suggest that BNM may exhibit a more aggressive clinical course, with earlier metastatic spread compared to other melanoma subtypes.[4] However, an Australian case series of 23 cases found no significant difference in metastatic potential or overall mortality compared to other melanomas.[3] The perception of increased aggressiveness may instead reflect delayed presentation and diagnosis in affected patients.[4] Owing to its rarity, large-scale studies aimed at identifying key prognostic factors and guiding treatment strategies remain challenging to conduct.

Conclusion

This case underscores the potentially aggressive nature of BNM, particularly in patients who present with metastatic disease. The absence of BRAF and NRAS mutations highlights the molecular heterogeneity of BNM and the limited therapeutic options currently available, emphasizing the urgent need for further research into targeted therapies and prognostic biomarkers for this rare melanoma variant.

Potential conflicts of interest

The authors declare no conflicts of interest.

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