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Melanoma ex blue nevus with *GNA11* mutation and *BAP1* loss: case report and review of the literature

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Abstract

Cutaneous melanomas may demonstrate a variety of histopathological features and genetic abnormalities. Melanomas that arise in the setting of blue nevi, also known as “malignant blue nevus” or melanoma ex blue nevus (MBN), share similar histopathological and mutational profile with uveal melanoma. The majority of uveal melanomas show characteristic *GNA11* or *GNAQ* mutations; additional *BAP1* mutation or loss is associated with the highest risk for metastasis and worst prognosis. However, the significance of *BAP1* loss in melanomas ex blue nevus remains unclear. We present a case of melanoma ex blue nevus arising from the scalp of a twenty-one-year-old female. The diagnosis was established on histopathological findings demonstrating a markedly atypical melanocytic proliferation with increased mitotic activity, necrosis, and a focus of angiolymphatic invasion. Immunohistochemical analysis demonstrated the absence of *BAP1* nuclear expression within tumor cells. Next Generation Sequencing detected *GNA11* Q209L mutation and *BAP1* loss (chromosome 3p region loss), supporting the diagnosis. We reviewed another twenty-one MBN cases with reported *BAP1* status from the literature. MBN with *BAP1* loss presented at a younger average age (41 years versus 61 years), demonstrated larger average lesion thickness (9.0 mm versus 7.3 mm), and had a higher rate of metastasis (50% versus 33%) compared with *BAP1*-retained MBN. *BAP1* expression studies may assist in the diagnosis and management of MBN, but further research is needed.

Keywords

melanoma ex blue nevus; malignant blue nevus; *BAP1* loss; melanoma

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Introduction

Blue nevi are a heterogeneous group of tumors that arise in the dermis from spindle and dendritic melanocytes. The majority of blue nevi are benign, but rarely malignant melanoma may show histologic features of a blue nevus or arise within a blue nevus.[1] Melanomas ex blue nevus (also known as “malignant blue nevus”) tend to affect younger adults and are usually located on the scalp.[2] Distinguishing them from benign lesions or metastatic melanoma may be challenging on histological grounds. We present a case of a melanoma ex blue nevus and discuss how Next Generation Sequencing (NGS) and *BAP1* expression status may be helpful in the diagnosis and management of these lesions.

Case Report

A twenty-one-year-old female presented with a five-month history of a two-centimeter blue/black subcutaneous nodule on the scalp (Fig. 1). The lesion had been gradually enlarging and becoming tender. The patient denied family history of melanoma, mesothelioma or renal cell carcinoma. A biopsy from the lesion revealed a broad and poorly demarcated intradermal proliferation composed of sheets and infiltrative fascicles of markedly atypical melanocytes that were epithelioid to fusiform in shape (Fig. 2A). These cells had enlarged, pleomorphic, vesicular nuclei, prominent nucleoli, and ample cytoplasm with dusty melanin (Fig. 2B). Scattered background melanophages with heavy pigmentation, areas of rhabdoid cytological features and conspicuous increased mitotic activity (3 mitosis/mm2) were noted. Tumor cells were diffusely positive for Sox-10 and Melan-A (Fig. 2C). Ki-67 stain demonstrated a high proliferative index. Based on these findings, a diagnosis of primary or metastatic malignant melanoma was rendered. To further classify the nature of the lesion, NGS was performed and revealed *GNA11* Q209L mutation, loss of short arm of chromosome 3 (3p) that harbors *BAP1* gene, and copy number gain of chromosome 8q region harboring the *MYC* gene. Immunohistochemical analysis confirmed the loss of *BAP1* nuclear expression within the tumor cells (Fig. 2D). *EWSR1* fluorescence in situ hybridization (FISH) study was performed to exclude clear cell sarcoma and was negative for rearrangement. Based on these molecular and immunohistochemistry findings, a diagnosis of a melanoma ex blue nevus with *BAP1* loss was established.

The patient underwent wide local excision of the lesion with two-centimeter margins. The excision specimen demonstrated an invasive atypical intradermal melanocytic tumor with a maximum thickness of 9.5 millimeters (Fig. 3). Large areas of necrosis, atypical cell morphology (rhabdoid, epithelioid, fusiform), increased mitotic activity and focal angiolymphatic invasion were seen in the re-excision specimen. Computed tomography (CT) of chest, abdomen and pelvis, and magnetic resonance imaging (MRI) of the brain revealed no regional or distant metastases. Dilated ophthalmic exam was negative for choroidal lesions. Dissection of three left cervical draining lymph nodes revealed no metastatic disease. Follow up brain and neck MRI eight months after the initial diagnosis was negative for metastatic disease. No evidence of recurrence was detected ten months after the wide local excision.

Discussion

The term “malignant blue nevus” was first used in 1953 to describe malignant melanoma arising within a cellular blue nevus.[1] Since then, other terms such as “melanoma associated with blue nevus,” “blue nevus-like melanoma” and “melanoma ex blue nevus” have been used to imply this entity.

Histopathologically, melanoma ex blue nevus may be difficult to distinguish from metastatic melanoma, pigmented epithelioid melanocytoma, and atypical spitzoid or atypical deep penetrating melanocytic tumors.[3] However, it is essential to classify melanocytic lesions accurately for correct clinical management. A case series of thirty-three melanocytic lesions with features of blue nevi demonstrated that, notwithstanding their morphology, some lesions harbored *BRAF*^{V600E} mutation and would have been better classified as atypical common nevi or conventional melanomas.[4]

Genetically, blue nevi and melanomas ex blue nevus are distinct from epidermis-derived common acquired nevi or “conventional” malignant melanoma, and are more closely related to uveal melanoma. Common acquired nevi and melanomas frequently harbor *BRAF* or *NRAS* mutations, but the majority of blue nevi carry *GNAQ* or *GNA11* mutations, similar to uveal melanoma.[5] *GNAQ* and *GNA11* are components of G proteins, and mutations in these genes activate the downstream mitogen-activated protein kinase (MAPK) pathway, leading to melanocytic proliferation. *BRAF* and *NRAS* mutations also activate the MAPK pathway. Mutations in *BRAF/NRAS* and *GNAQ/GNA11* have been shown to be mutually exclusive in melanocytic lesions.[6]

In uveal melanoma, loss of *BAP1* (*BRCA1* associated protein 1), a tumor suppressor gene, due to a mutation or deletion or loss of chromosome 3, is associated with the highest rate of metastasis and worst prognosis. Germline mutations in *BAP1* have been identified in familial syndromes with an increased incidence of uveal melanoma, cutaneous melanoma, mesothelioma, renal cell carcinoma, and atypical melanocytic tumors, known as *BAP1* inactivated melanocytic tumor.

Little is known about the significance of *BAP1* loss in melanomas ex blue nevus. A previous study showed that the loss of chromosome 3p region was detected in three of nine melanoma ex blue nevus, but in none of the seventeen blue nevi cases.[7] In another study, the loss of *BAP1* expression was found exclusively in malignant but not in benign counterparts of this blue nevi family. Three melanoma ex blue nevus that developed distal metastases all demonstrated *BAP1* loss.[2] The authors predict that melanomas ex blue nevus with *BAP1* loss may have aggressive behavior and greater metastatic potential, similar to uveal melanoma.

We reviewed an additional twenty-one melanoma ex blue nevus cases previously published in the literature with known *BAP1* status (Table 1). In these twenty-two cases (including our case), the average age at presentation of tumors with and without *BAP1* loss was 41 versus 61 years. The average tumor thickness of melanomas with and without *BAP1* loss was 9.0 mm versus 7.3 mm. The incidence of metastases developed in melanomas with and without *BAP1* loss were 50% (5/10) versus 33% (3/9). The time to the development of metastases

ranged from 19 to 144 months. In uveal melanoma, one early study showed that 57% of thirty patients with the loss of one chromosome 3 region relapsed with metastatic disease; none of the twenty-four patients without the chromosome 3 loss developed metastatic disease.[8] These data suggest that loss of *BAP1* expression in melanoma ex blue nevus may be an important prognostic factor with potential for metastasis similar to uveal melanoma. In addition, *BAP1* loss by immunohistochemistry is a very useful diagnostic marker while dealing with atypical blue nevi tumors. These results deserve further validation and investigation using larger cohorts.

Very few studies have compared clinical outcomes of conventional melanomas and melanoma ex blue nevus with similar disease burden. It remains unclear whether the prognostic factors for conventional cutaneous melanoma are applicable to melanomas with *GNAQ/GNA11* mutations. One study that reviewed ten melanoma ex blue nevus cases suggested these lesions were highly aggressive tumors with a propensity for metastasis.[9] Further studies compared cohorts of conventional and *GNAQ/GNA11* mutated melanomas with similar tumor burden showed despite presenting at an advanced stage, the clinical course and survival rate of melanoma ex blue nevus resembled those of conventional melanoma.[10,11] Another study analyzed twenty-one melanoma ex blue nevus cases and found a significant correlation between tumor thickness and recurrence-free survival; other clinicopathological parameters such as anatomic location, lymphovascular invasion and perineural invasion did not show significant prognostic association.[12] These results suggest that melanoma ex blue nevus should be managed similarly to conventional melanoma, but this recommendation needs to be validated by larger cohorts.

In conclusion, we herein describe a case of melanoma ex blue nevus arising from the scalp of a young female harboring *GNA11* mutation and loss of *BAP1* expression. The malignant nature of this melanocytic tumor was established based on marked histological atypia, high mitotic and proliferation index, large areas of necrosis and angiolymphatic invasion. NGS and *BAP1* expression studies assisted in the further classification of the disease and subsequently appropriate management. *BAP1* expression may have an important implication on the prognosis of this family of malignant lesions. However, further studies on larger cohorts are necessary to validate these results.

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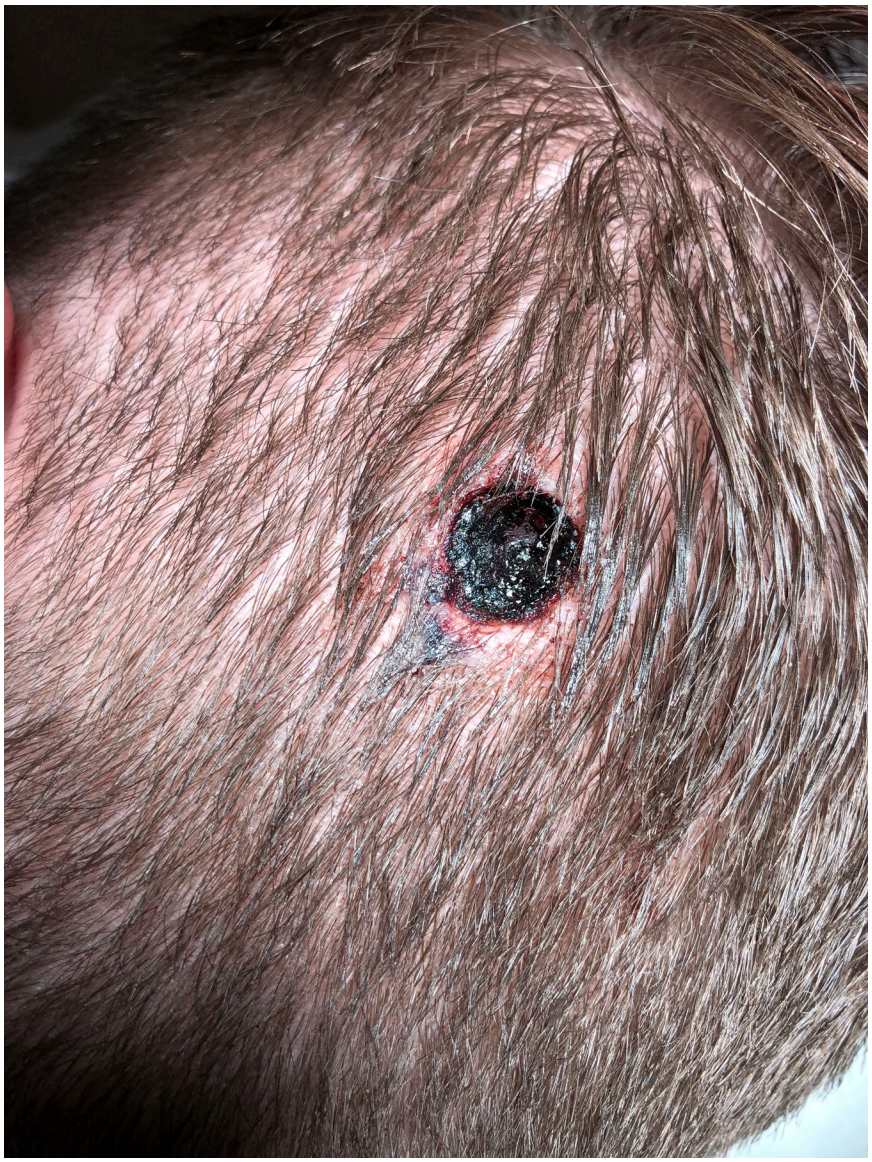

Figure 1.
Image taken after the biopsy of the lesion. Initial presentation revealed a two-centimeter blue/black subcutaneous nodule on the left occipital scalp of a twenty-one year-old female.

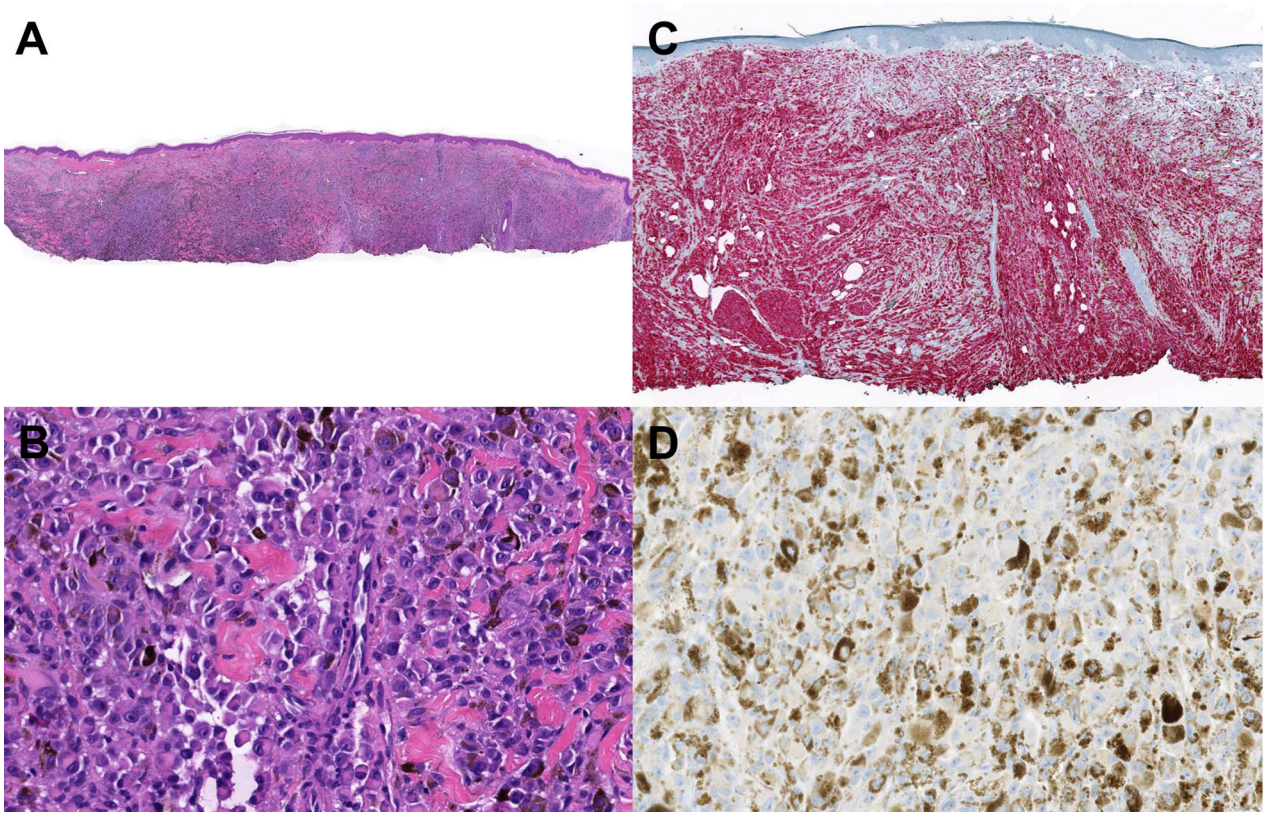

Figure 2.

Histolopathologic examination of the biopsied lesion. (A) Scanned and cropped H&E slide showing a melanocytic lesion with sheet-like atypical melanocytes and heavy pigmentation. (B) Scanned and cropped H&E slide with a higher magnification demonstrating atypical melanocytes with a rhabdoid morphology. (C) Melan-A immunostaining showing diffuse expression of Melan-A immunostain in the tumor. (D) *BAP1* immunostaining showing loss of nuclear *BAP1* expression in melanoma cells.

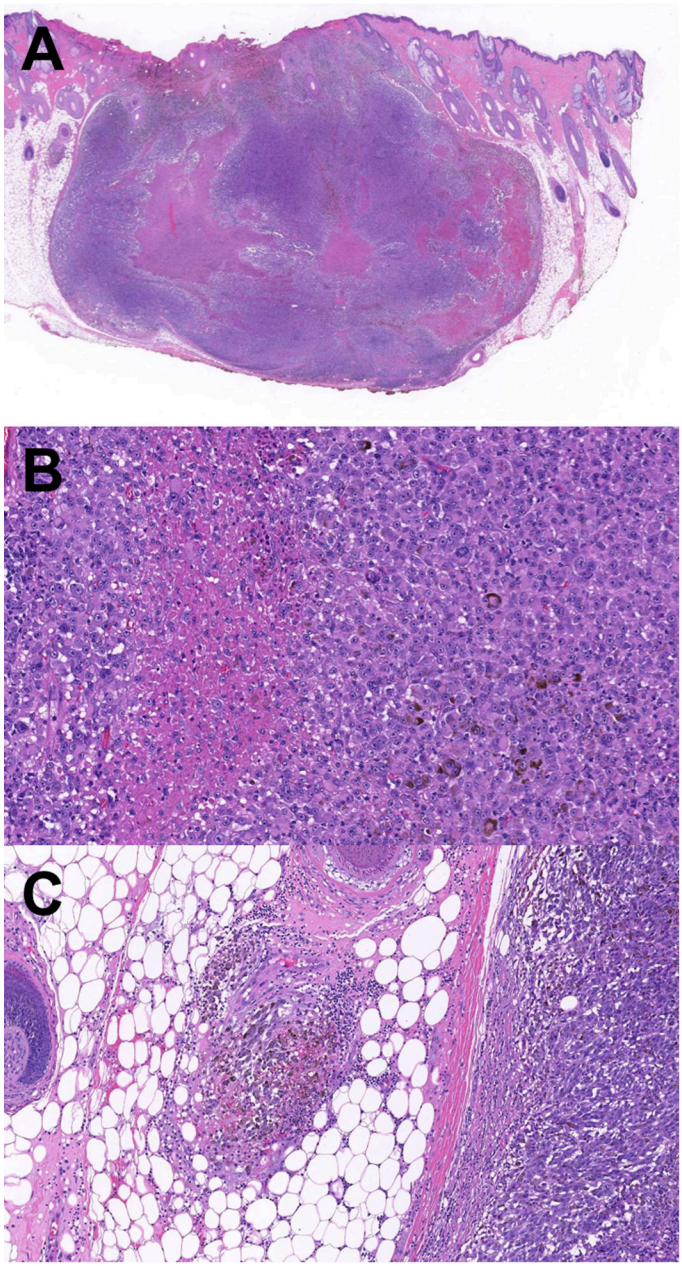

Figure 3.

Histopathologic examination of the re-excision specimen. (A) Re-excision of the neoplasm demonstrating a large nodule with extensive necrotic areas. H&E stain, scanned and cropped image. (B) Higher magnification shows necrotic areas and sheets of highly atypical pigmented melanocytes. H&E stain, scanned and cropped image. (C) A destroyed vessel with angioinvasion at the vicinity of the melanoma. H&E stain, scanned and cropped image.

Table 1.

Twenty-two published malignant blue nevi cases that have available *BAP1* expression status based on immunohistochemical staining. Nineteen of these cases have clinical follow-up data.

	Case	Age	Sex	Site	Follow-up (mo)	Outcome	Metastasis	Thickness (mm)	*BAP1* Status	*GNA11/ GNAQ* Mutation
Yeh 2014[13]	1	64	F	Scalp	22	No evolution of disease	None		Loss	Not tested
Dai 2016[14]	1	46	F	Scalp	72	Died from complications of sepsis	Liver metastasis		Loss	*GNA11*
Costa 2016[2]	1	21	M	Scalp	19	Died of disease	Liver metastasis	5	Loss	*GNA11*
	2	26	M	Scalp				7	Loss	*GNA11*
	3	27	F	Shoulder	74	Died of disease	Widespread metastasis	7	Loss	*GNA11*
	4	36	F	Scalp	18	No evolution of disease	Cervical lymph node metastasis	13	Loss	*GNA11*
	5	49	M	Scalp	6	No evolution of disease	None	7	Loss	*GNA11*
	6	49	F	Scalp	29	Stable disease	None	14	Loss	WT
	7	82	F	Scalp	18	No evolution of disease	None	9.2	Loss	WT
	8	56	M	Scalp	23	No evolution of disease	None	20	Normal	*GNA11*
	9	69	F	Scalp	3	No evolution of disease	None	6	Normal	*GNAQ*
	10	75	F	Scalp	24	No evolution of disease	None	8	Normal	*GNA11*
	11	79	F	Scalp	4	No evolution of disease	None	7.4	Normal	*GNA11*
Griewank 2017[4]	22	88	M	Scalp	30	Died of Alzheimer's, HF and metastatic disease	Metastatic disease		Normal	WT
	23	61	M	Scalp	72	Died of disease	Metastatic disease		Normal	*GNA11*
	26	35	M	Gluteal region	13	No evolution of disease	None	6	Normal	*GNAQ*
	27	39	M	Scrotum	4	No evolution of disease	None		Normal	*GNA11*
	36	64	M	Temporal	144	Cervical lymph node metastasis	Neck soft tissue metastasis	7.5	Normal	*GNA11*
	37	66	M	Pectoral				1.45	Normal	*GNA11*
	38	31	M	Temporal	103	Progressive disease	Widespread disease		Loss	*GNA11*
Castillo 2018[15]	1	39	M	Scalp				2.1	Normal	*GNAQ*
This report	1	21	F	Scalp	10	No evolution of disease	None	9.5	Loss	*GNA11*