

Melanoma Arising in Blue Nevus: A Case Report Demonstrating the Primary Site in Disseminated Disease

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Abstract

Blue nevus is a benign dermal lesion occasionally associated with malignant transformation into melanoma arising in a blue nevus, a rare and aggressive form of melanoma with different molecular features. Fewer than 200 cases have been reported worldwide. In this case study, a 78-year-old woman presented with a congenital bluish nodular lesion on the left buttock that enlarged over the years. Magnetic resonance imaging suggested a malignant soft tissue tumor. Surgical excision was performed, accompanied by an intraoperative histopathological study, reporting a melanoma with no dermoepidermal junction involvement. Immunohistochemistry confirmed the melanocytic origin; molecular analysis ruled out a *BRAF* gene mutation but identified a *GNAQ* exon 5 mutation in the melanoma and blue nevus components, confirming the precursor lesion. Despite multiple therapies, the disease progressed with metastases to the liver, lungs, and brain, ultimately resulting in the patient's death. Melanoma arising in a blue nevus represents an aggressive neoplasm, highlighting the importance of early biopsy and multidisciplinary evaluation. The application of immunohistochemistry and molecular profiling in atypical presentations that mimic other neoplasms represents a valuable tool for diagnosis, prognosis, and treatment planning in rare melanoma subtypes.

Categories: General Surgery, Pathology, Dermatology

Keywords: bap1, blue nevus, braf mutation, gnaq mutation, melanoma

Introduction

Blue nevus (BN) is a benign proliferation of dermal melanocytes. It typically arises in areas where residual dermal melanocytes persist from embryogenesis, such as the sacrum, distal extremities, scalp, and trunk [1-3]. It is characterized by a solitary, homogeneous, circumscribed, blue-gray, blue-brown, or blue-black macule or papule, distinguishing it from other pigmented lesions [2,3]. There are two types of BN, the dendritic type, which presents during adolescence measuring <1 cm; and the cellular BN, a congenital or acquired larger neoplasm (≥1 cm) [4]. Histopathologically, BN shows spindle-shaped or dendritic melanocytes located in the dermis, expressing HMB45, MELAN-A, or tyrosinase markers [5]. Additionally, the molecular profile of BN includes somatic activating mutations in the *GNAQ* and *GNA11* genes [5]. BN management is conservative; however, sudden onset or clinical changes, such as enlargement, change in color, bleeding, or ulceration, prompt histopathological evaluation to exclude malignant transformation. Although rare, some cases of melanoma arising in blue nevus (MBN) have been reported [1,6,7].

MBN is a rare and aggressive tumor, with fewer than 200 cases described worldwide, typically originating from a cellular BN and presenting as a rapidly growing nodule in adults [7]. It is also associated with mutations in the *GNAQ* and *GNA11* genes, which may harbor BAP1, SF3B1, or PRKAR1A alterations [8]. It exhibits aggressive behavior with a high risk of metastasis, resulting in poor clinical outcomes [3].

In this case, a 78-year-old female presented with a left gluteal mass diagnosed as MBN. Despite treatment, the neoplasm showed aggressive behavior with an unfavorable clinical course. Initially, based on clinical and imaging findings, it was suspected to be a sarcoma; however, intraoperative histopathology revealed a melanoma lacking dermoepidermal junction involvement. The primary cutaneous origin from a BN was confirmed through molecular profiling, highlighting the diagnostic utility of these tools in cases of disseminated disease. This report aims to illustrate the diagnostic challenges and molecular confirmation of MBN, particularly in the context of disseminated disease.

Case Presentation

A 78-year-old woman presented with a pruritic, bluish, nodular tumor on the left buttock that had been present since birth and had enlarged over the previous three years. The patient denied changes in lesion color or systemic symptoms, such as weight loss, fever, or infection. Her past medical history was unremarkable with no family history of melanoma or similar lesions among first-degree relatives. Physical

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examination revealed a 5-cm bluish, nodular lesion with regular borders, not adherent to deeper tissues, in the left gluteal region. An initial diagnosis of lipoma was considered; however, ultrasonography (USG) demonstrated a vascularized subcutaneous lesion, raising concern for a neoplastic process (Figure 1). Pelvic magnetic resonance imaging (MRI) demonstrated an enhancing soft tissue lesion suspicious for sarcoma (Figure 2).

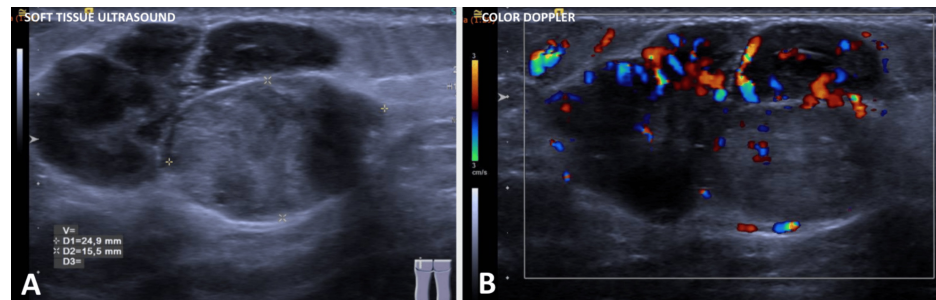


FIGURE 1: USG of the left gluteal lesion showing a heterogeneous subcutaneous lobulated mass; the largest lobe measuring 24.9×15.5 mm (yellow measurement calipers) (A), with central and peripheral vascularity on Doppler (B).

USG: ultrasonography, D1: longest axis of the largest lobe, D2: shortest axis of the largest lobe.

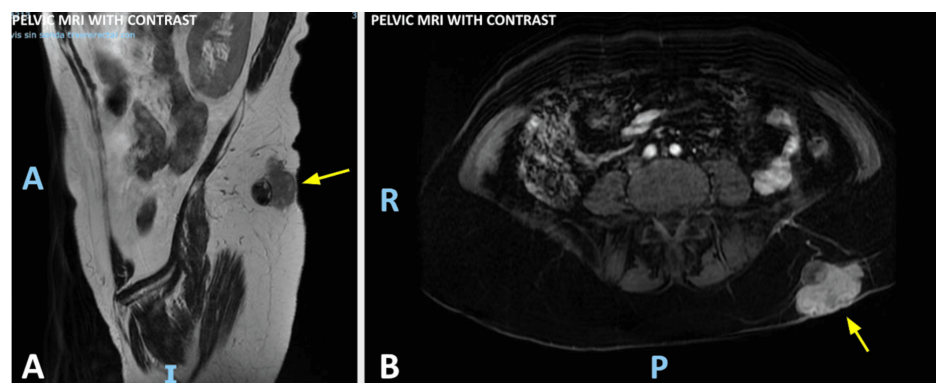


FIGURE 2: Sagittal (A) and axial (B) pelvic MRI demonstrating a 5.5×3.8 cm enhancing superficial left gluteal adipose tissue lesion, with cystic changes (yellow arrows).

MRI: magnetic resonance imaging.

Complete surgical excision was performed, and intraoperative examination revealed a nodular melanoma with epithelioid and fusiform patterns arising within a pre-existing BN (Figure 3). Areas consistent with BN were identified, composed of ovoid melanocytic cells arranged in nests, showing minimal atypia, low mitotic rate, and absence of necrosis. The melanoma component consisted of large spindled and epithelioid cells with moderate atypia and pigmented melanophages with two macroscopic satellite nodules.

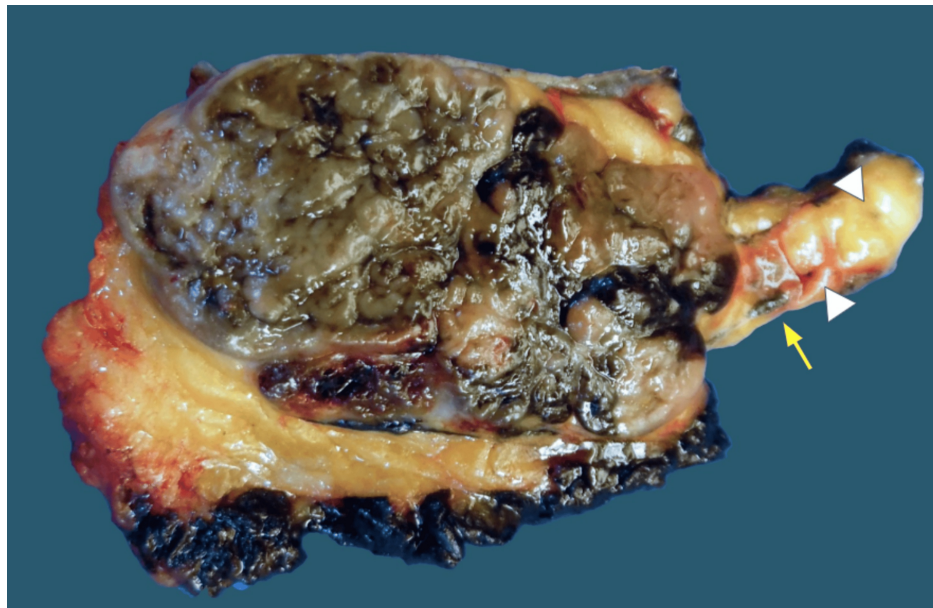


FIGURE 3: Gross features of melanoma arising in blue nevus (main tumor mass 5.7 x 3.8 cm).

Cut surface showing a large, nodular, uniform and pigmented tumor (satellite nodule measuring 0.5 x 0.4 cm - yellow arrow) and dark small spots corresponding to blue nevi (white arrowheads).

Immunohistochemical analysis confirmed melanocytic differentiation, with a high proliferative index (Ki67 30%), and retained BAP1 expression (Figure 4). This finding is relevant, as BAP1 loss is typically associated with aggressive behavior in melanocytic tumors arising from blue nevi, whereas retained expression suggests a distinct molecular profile with different outcomes [8]. Molecular analysis demonstrated a *GNAQ* exon 5 mutation and absence of *BRAF* mutations in the melanoma and BN, supporting a clonal relationship and malignant transformation of a pre-existing BN (Figure 5).

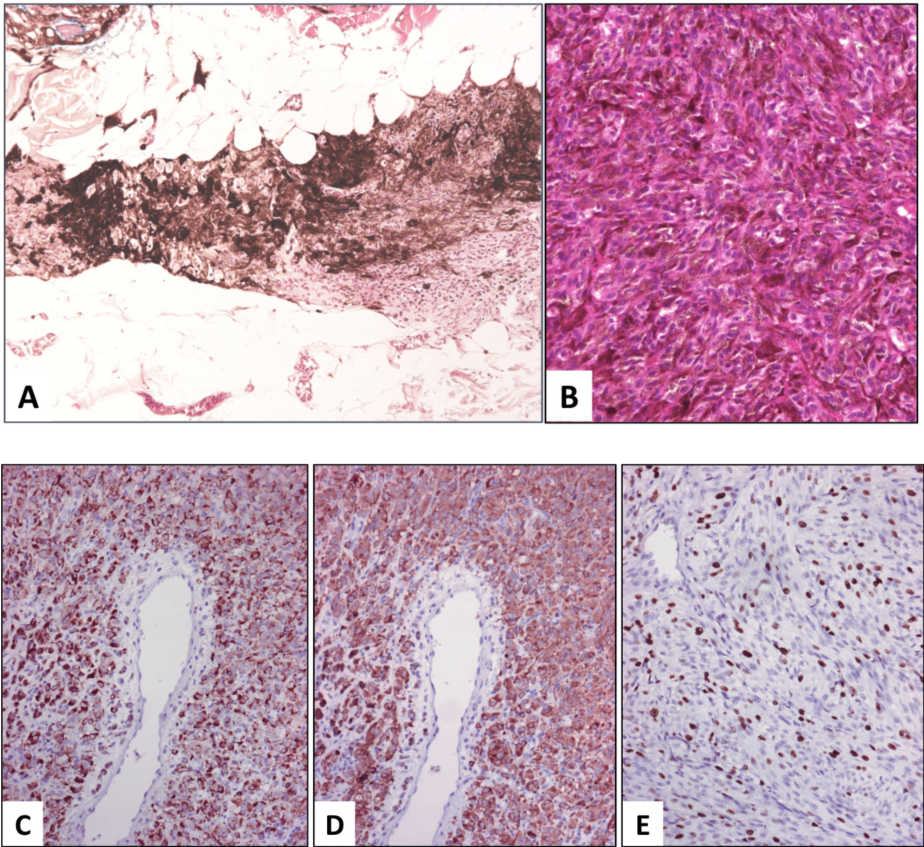


FIGURE 4: Microscopic features of precursor lesion and melanoma.

Frozen section showing fusiform pigmented cells surrounded by adipose tissue at 10X magnification (A). Hematoxylin and eosin–stained slide showing a hypercellular melanoma lesion with epithelioid and spindle cell patterns, cellular atypia and mitotic figures at 40X magnification (B). Positive HMB45 at 40X magnification (C). Positive MELAN-A at 40X magnification (D). Ki67 30% at 40X magnification (E).

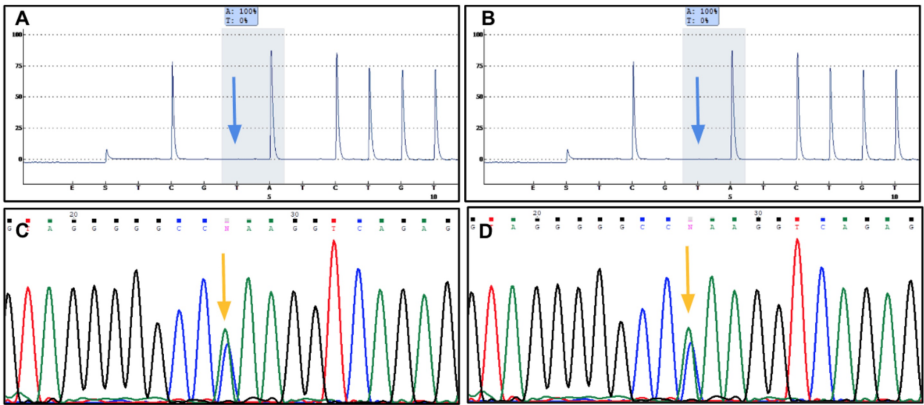


FIGURE 5: Mutation analysis of V600E of the BRAF gene by pyrosequencing and GNAQ gene by Sanger sequencing in the blue nevus and melanoma.

A: adenine, T: thymine.

Pyrosequencing of the *BRAF* gene in blue nevus (A) and melanoma (B) on the reverse strand of the *BRAF* gene; both with 0% frequency of the mutant T allele (blue arrows). Sanger sequencing of exon 5 of *GNAQ* gene in blue nevus (C) and melanoma (D); both showing the c. 262A>C p.Q209P somatic mutation (yellow arrows).

Baseline positron emission tomography-computed tomography (PET-CT) revealed a postoperative, non-

metabolically active gluteal seroma and subcentimetric pulmonary nodules (<1 cm) without metabolic activity; given the absence of smoking history or underlying pulmonary disease, these nodules were considered indeterminate and scheduled for radiologic surveillance. Serum lactate dehydrogenase (LDH) and S100 levels and programmed-death ligand 1 (PD-L1) expression were not assessed at diagnosis, and baseline central nervous system imaging was not performed in the absence of neurological symptoms.

Two months after initial excision, wide local re-excision with sentinel lymph node biopsy was performed. Surgical margins were negative and one of two sentinel lymph nodes demonstrated metastatic involvement, consistent with stage IIIC melanoma.

Within three months after surgery, follow-up fluorine-18 fluorodeoxyglucose (18F-FDG) PET-CT demonstrated progressive metastatic disease involving the left adrenal gland, consistent with stage IV melanoma (Figure 6). Treatment with intravenous nivolumab (480 mg every four weeks) was initiated but discontinued after two cycles due to grade 3 immune-mediated hepatitis, managed with high-dose prednisone (50 mg daily), resulting in clinical and biochemical improvement. Stereotactic body radiotherapy (SBRT) was subsequently administered to the adrenal lesion, delivering a total dose of 35 Gy in five fractions, achieving local disease control.

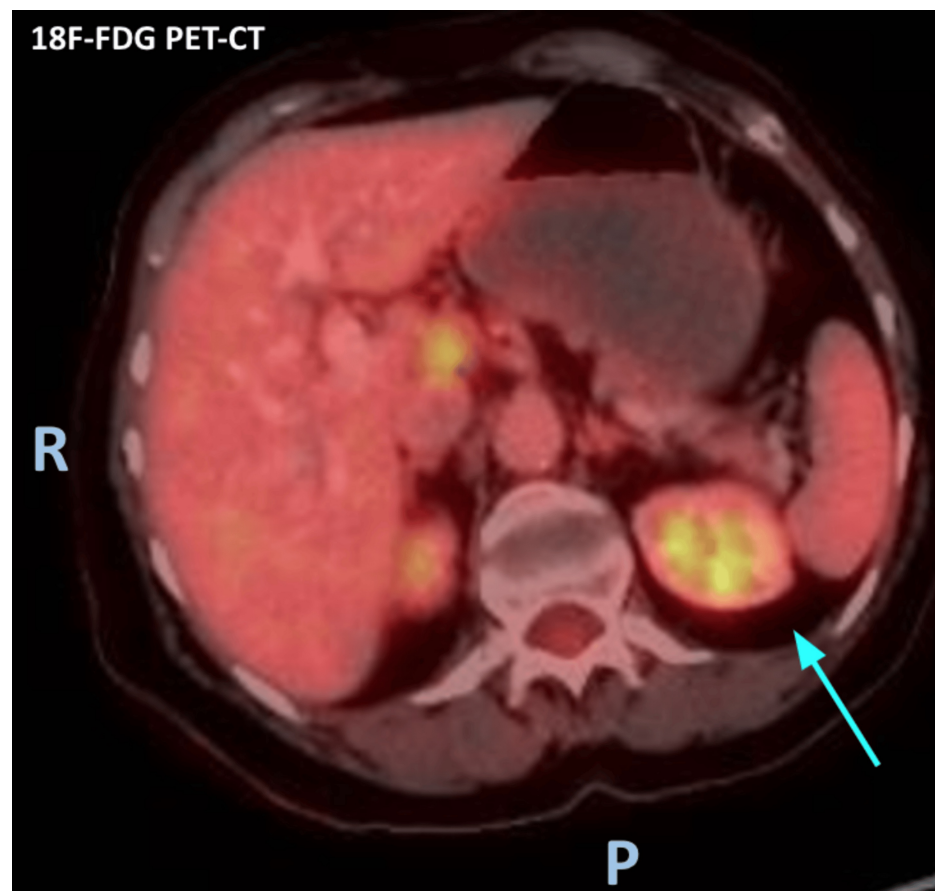


FIGURE 6: 18F-FDG PET-CT scan demonstrating hypermetabolic involvement of the left adrenal gland (blue arrow).

18F-FDG PET-CT: fluorine-18 fluorodeoxyglucose positron emission tomography–computed tomography.

Follow-up imaging at six months post-surgery showed no evidence of disease; nevertheless, at 12 months post-surgery, hepatic metastases were identified. Second-line therapy with oral temozolomide was initiated at a dose of 200 mg/m² days one through five of a 28-day cycle; however, due to hematologic and hepatic toxicity, the dose was subsequently reduced to 150 mg/m².

At 15 months post-surgery, disease progression with pulmonary and hepatic metastases was documented. Reintroduction of immunotherapy with corticosteroid prophylaxis or chemotherapy with nab-paclitaxel were considered; however, both options were excluded due to persistent hematologic and hepatic toxicity, as well as the patient's preference for palliative care. As a palliative measure aimed at preserving quality of life, intravenous carboplatin was administered on a fractionated schedule every 21 days for four cycles.

Despite systemic therapy, at 19 months post-surgery, serial PET-CT demonstrated progressive metastatic dissemination (Figure 7). Two months later (21 months post-surgery), the patient presented with hemoptysis. Computed tomography pulmonary angiography (CTPA) revealed progressive pulmonary metastases (Figure 8). Bronchoscopy revealed an actively bleeding obstructing tumor in the left upper lobe bronchus. Electrocauterization successfully controlled the bleeding, followed by palliative thoracic radiotherapy (30 Gy in 10 fractions).

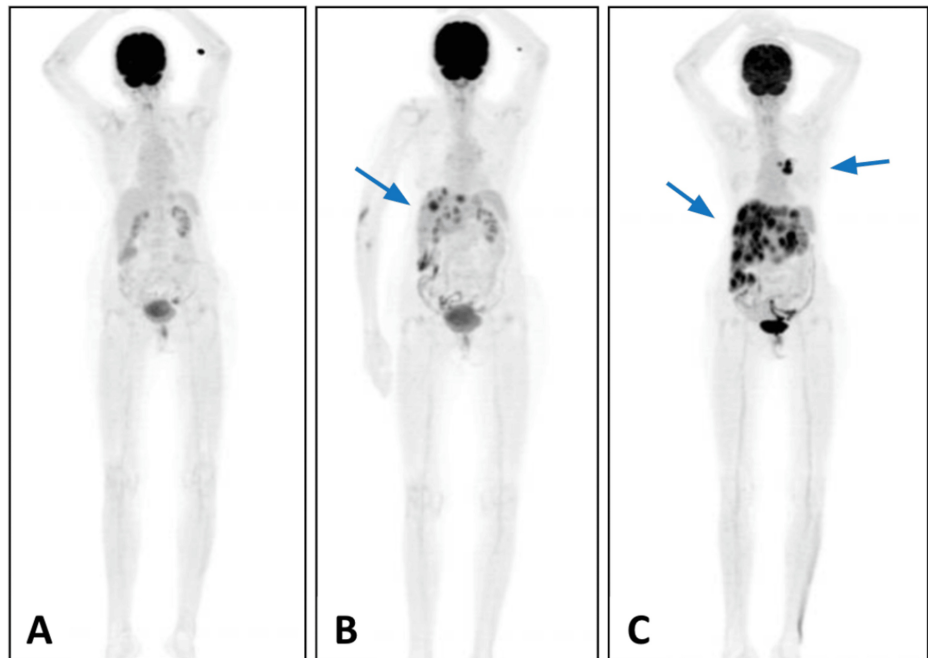


FIGURE 7: Serial whole-body PET-CT follow-up studies showing progressive metastatic disease over time.

PET-CT: positron emission tomography–computed tomography.

Whole-body PET-CT follow-up. No evidence of disease at 6 months post-surgery (A). Disease progression at 15 months with hepatic involvement (B). Further progression at 19 months with extensive hepatic metastases, mediastinal lymphadenopathy, and a left diaphragmatic implant (C).

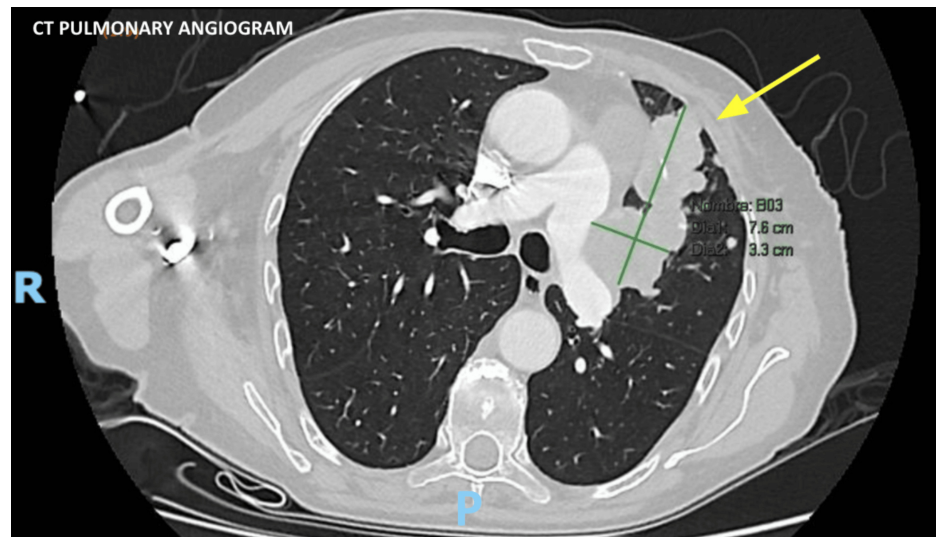


FIGURE 8: CTPA showing solid pulmonary and mediastinal lesions consistent with metastatic disease progression; the largest lesion (7.6 x 3.3 cm) extending from the hilum (yellow arrow).

CTPA: computed tomography pulmonary angiogram, Nombre: B03: identifier of the lesion, Dia1: diameter of longest axis, Dia2: diameter of shortest axis.

One month later (22 months post-surgery), the patient developed signs of cerebellar syndrome. Brain computed tomography demonstrated multiple cerebral and cerebellar metastases (Figure 9). Palliative whole-brain radiotherapy (24 Gy in eight fractions) was initiated but discontinued due to rapid neurological deterioration. At 23 months post-surgery, the patient developed brief focal impaired-awareness seizures with disorientation, progressive weakness, and systemic decline, and died shortly thereafter. A timeline of the clinical course is shown in Table 1.

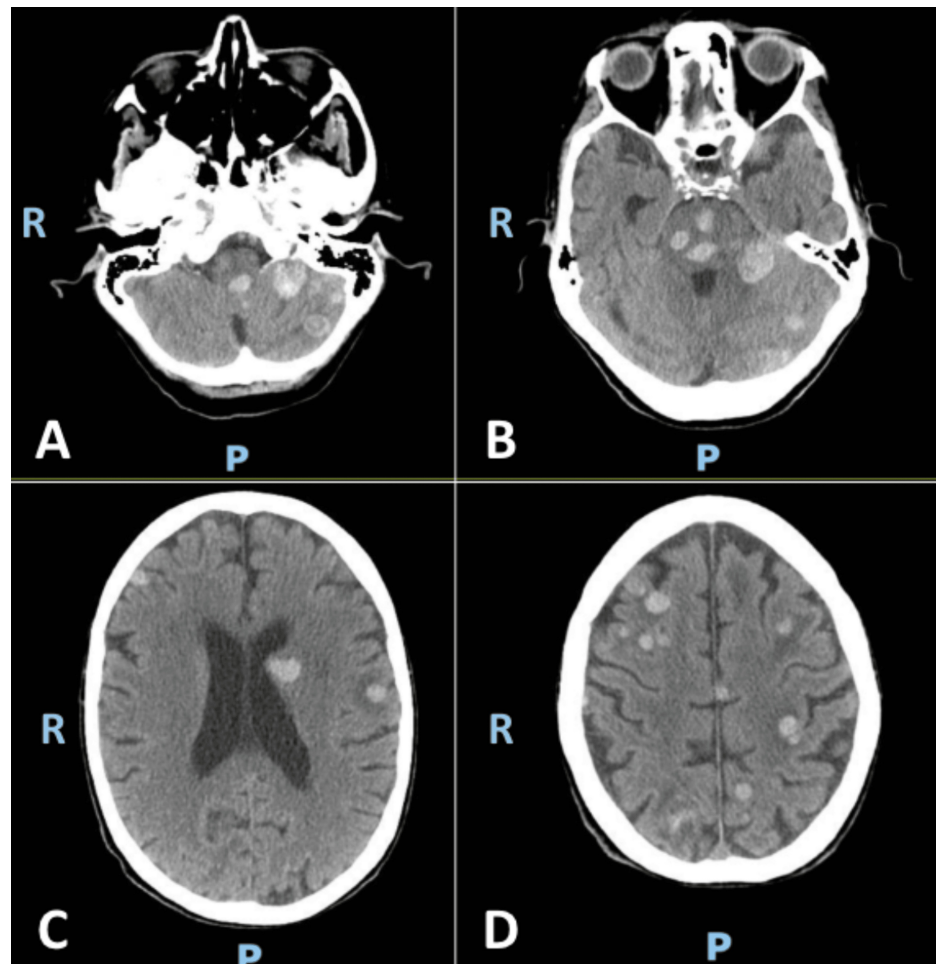


FIGURE 9: Brain computed tomography with contrast after 22 months of melanoma arising in blue nevus (MBN) diagnosis.

Brain metastasis involving the cerebellum (A), brainstem (B), basal ganglia (C) and cortex (D).

Time from initial surgery	Clinical event	Treatment	Disease status	Outcome / response
Initial surgery	Complete excision of primary lesion	Surgical excision	Localized disease	—
2 months	Wide local re-excision and sentinel lymph node biopsy	Surgery	1/2 sentinel lymph nodes positive (Stage IIIC)	Surgical margins negative
~3 months	New hypermetabolic lesion in left adrenal gland on PET-CT	Nivolumab 480 mg IV every 4 weeks (2 cycles)	Progression to Stage IV	Treatment discontinued due to grade 3 immune-mediated hepatitis
~4 months	Persistent adrenal metastasis	SBRT to left adrenal gland (35 Gy in 5 fractions)	Oligometastatic disease	Local disease control
6 months	PET-CT follow-up	—	No evidence of active disease	Stable
12 months	New hepatic metastases	Temozolomide 200 mg/m ² (days 1–5, q28 days); dose reduced to 150 mg/m ²	Metastatic progression	Disease progression; treatment limited by toxicity
15 months	Progressive hepatic and pulmonary metastases	Carboplatin (AUC 5) every 21 days × 4 cycles	Persistent metastatic disease	Temporary stabilization
19 months	New mediastinal lymph nodes and diaphragmatic implant on PET-CT	—	Disease progression	Progression
21 months	Hemoptysis due to obstructive endobronchial tumor	Endobronchial electrocautery + palliative thoracic radiotherapy (30 Gy in 10 fractions)	Progressive pulmonary disease	Bleeding controlled
22 months	Cerebellar syndrome	Whole-brain radiotherapy (24 Gy in 8 fractions; discontinued)	Cerebral and cerebellar metastases	Neurological deterioration
23 months	Systemic decline	Best supportive care	Advanced metastatic disease	Death

TABLE 1: Timeline of disease progression, treatments, and clinical outcomes

SBRT: stereotactic body radiotherapy, PET-CT: positron emission tomography computed tomography, Gy: Gray, Fx: fractions, AUC: Area Under the Curve, RT: radiotherapy, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

Discussion

MBN is an uncommon melanoma subtype with a genetically distinct profile that typically originates from a cellular BN, and often presents with atypical clinical and histopathological features, as observed in the present case [4]. It is a rare malignant neoplasm, with fewer than 200 cases reported worldwide [7]. Clinically, MBN presents as a rapidly enlarging dermal nodule in regions such as the head, neck, trunk, or buttocks, most commonly in middle-aged adults [7]. Unlike conventional cutaneous melanoma, MBN is driven by somatic activation of the Gαq signaling pathway, commonly through mutations in GNAQ (>50%) or GNA11 (~15%) genes, rather than BRAF mutations (<20%) [8-10], which limit targeted therapeutic options and contribute to poorer outcomes [11].

From a molecular standpoint, BN and MBN share overlapping genetic features; BN typically harbors somatic mutations in GNAQ (~83%) or GNA11 (~15%), and less frequently in KRAS (3%), CYSLTR2 (3%), or PLCB4 (3%) genes [5,9-13]. In addition to GNAQ/GNA11 alterations, MBN may also present mutations in PLCB4 or CYSLTR2 genes, as well as SF3B1, PRKAR1A, or BAP1, which are associated with increased metastatic potential, particularly to lymph nodes and the liver [3,8,12,13]. In the present case, the identification of the GNAQ exon 5 mutation in both the BN and the melanoma supports a clonal relationship and confirms a malignant transformation of a pre-existing lesion. This finding is consistent with previous studies suggesting that GNAQ and GNA11 mutations represent early oncogenic events, persisting throughout

malignant transformation, rather than acting as late driver mutations [8,11,13].

Furthermore, the role of BAP1 in MBN remains under active investigation; the loss of BAP1 expression has been correlated with more aggressive behavior and poorer prognosis in MBN, similar to what has been described in uveal melanoma [8]. Conversely, BAP1 retention, as observed in our patient, may correlate with a less aggressive phenotype, although its prognostic value is not fully defined. Notably, despite BAP1 retention, our patient developed aggressive disease; therefore, BAP1 alone may not be sufficient to predict MBN clinical behavior. Recent studies suggest that BAP1 status may influence metastatic disease, especially in *GNAQ/GNA11*-mutated melanocytic tumors; however, conclusions are limited by small cohort studies [14].

Management of MBN can be challenging due to its low frequency and lack of therapeutic guidelines. Treatment generally follows that of high-risk cutaneous melanoma, including wide local excision, sentinel lymph node biopsy, and systemic therapies. In our patient, nivolumab was selected as first-line systemic therapy following progression to stage IV disease, consistent with treatment approaches for *BRAF* wild-type melanoma; nevertheless, PD-L1 expression and tumor mutational burden were not assessed, reflecting real-world clinical practice in which immunotherapy decisions are often made independently of these biomarkers. Although immunotherapy was discontinued due to grade 3 immune-mediated hepatitis, local disease control of the adrenal metastasis was achieved with radiotherapy, highlighting its role as an effective modality for oligometastatic control. Moreover, chemotherapy regimens demonstrated limited benefit, consistent with previous reports of poor outcomes in MBN treated with conventional cytotoxic agents [15].

This case emphasizes the diagnostic challenge of MBN. The lesion was not clinically suspected to be a melanoma; moreover, the final diagnosis was established incidentally during intraoperative examination, followed by molecular studies confirming a shared *GNAQ* mutation between the melanoma and the precursor lesion. These findings reinforce the value of integrating intraoperative morphological assessment and molecular analysis, which proved important in atypical dermal tumors that mimic other malignancies.

This case reinforces the importance of early histopathological and molecular evaluation in atypical dermal lesions, particularly in patients with a history of congenital or long-standing nevi.

Conclusions

MBN is a rare and aggressive melanoma subtype with distinct clinical, histopathological, and molecular characteristics. This case highlights the malignant transformation of a congenital BN into melanoma and emphasizes the importance of vigilant surveillance, biopsy, and molecular testing to guide personalized treatment and improve outcomes. Notably, the identification of melanocytic markers, a *GNAQ* mutation, and the absence of a *BRAF* mutation were critical for confirming the primary origin. This case underscores the value of a multidisciplinary diagnostic approach and the pivotal role of molecular profiling in distinguishing primary cutaneous melanomas from disseminated disease.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Liliana Perez-Limon, Armando Gamboa-Dominguez, Maria F. Contreras-Solis, Beatriz E. Sanchez-Hernandez

Acquisition, analysis, or interpretation of data: Liliana Perez-Limon, Armando Gamboa-Dominguez, Maria F. Contreras-Solis, Beatriz E. Sanchez-Hernandez

Drafting of the manuscript: Liliana Perez-Limon, Armando Gamboa-Dominguez, Maria F. Contreras-Solis, Beatriz E. Sanchez-Hernandez

Critical review of the manuscript for important intellectual content: Liliana Perez-Limon, Armando Gamboa-Dominguez, Maria F. Contreras-Solis, Beatriz E. Sanchez-Hernandez

Supervision: Liliana Perez-Limon, Armando Gamboa-Dominguez, Maria F. Contreras-Solis, Beatriz E. Sanchez-Hernandez

Disclosures

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