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Aggressive infantile melanoma arising in a congenital nevus with rare *BRAF* and *BCOR* mutations: a case report and literature review of pediatric melanoma

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Abstract

We report a case of aggressive melanoma in a 14-month-old girl, arising in a congenital nevus with multiple satellite lesions on the lower back and buttocks. The tumor exhibited a sarcomatous-like histology and harbored rare *BRAF* (p.Asp594Gly) and *BCOR* (p.Leu1480GlyfsTer11) mutations. Treatment included surgery and systemic therapies (nivolumab and ipilimumab, followed later by tovorafenib). Despite the initial response, the disease progressed rapidly with pulmonary metastases and lymphadenopathy. The patient's clinical course was marked by aggressive local progression and therapeutic challenges. This case highlights the rarity of such presentations and the need for further research into the clinicopathological and molecular features of infantile melanoma arising in congenital melanocytic nevus (CMN).

Introduction

Melanoma is one of the most common malignancies in adults; however, it remains rare in the pediatric population. In 2020, approximately 100,350 new melanoma cases were projected in the United States, with only around 500 occurring in individuals under the age of 20.[1] Pediatric melanoma represents approximately 1% of all childhood cancers, with a global incidence of 2-5 new cases per million individuals annually.[2] Among these cases, approximately 79% occur in adolescents, while only 0.3-0.4% present during the first decade of life.[3] Pediatric melanoma can be classified into four categories based on age at diagnosis: congenital (*in utero* to birth), infantile (birth to 1 year), childhood (1 year to puberty), and adolescent melanoma (puberty to 21 years). This classification reflects distinct differences in clinical presentation, biological behavior, and etiology across age groups. Congenital and infantile malignant melanomas are further subclassified based on origin into three categories: arising within congenital melanocytic nevi (CMN), arising *de novo* from normal skin, and resulting from transplacental metastasis of maternal melanoma.[4] Most pediatric melanomas arise in association with CMN.[5] The risk of melanoma is markedly elevated in individuals with large congenital melanocytic nevi (LCMN), particularly when the projected adult size exceeds 20 cm, and even more with nevi over 40 cm.[6,7] In contrast, small- and medium-sized CMN are associated with a significantly lower lifetime melanoma risk, generally estimated at less than 1%.[6,7] Nevi located on the trunk, especially in the "bathing trunk" distribution, are more prone to malignant transformation.[8] A key modifier of risk is the presence of numerous satellite nevi, which have been associated with higher risks of both cutaneous melanoma and neurocutaneous melanocytosis (NCM).[7] NCM is further linked to an increased risk of central nervous system (CNS) melanoma, which is notably aggressive.[7,8] Management of melanoma in children and

adolescents generally mirrors adult protocols, with surgical excision as the primary approach.[9] Wide local excision with histologically clear margins remains the standard treatment for primary melanoma.[9] Advanced or metastatic disease presents greater challenges, given the limited efficacy and significant toxicity of traditional chemotherapy. Targeted therapies, especially BRAF and MEK inhibitors, and immunotherapy have revolutionized adult melanoma treatment.[10] Although pediatric data are limited, these therapies are beneficial in selected cases. Molecular profiling is essential for tailoring treatment strategies in this population.[9,10]

Case Report

We report a 14-month-old girl who developed multiple CMN on her lower back and buttocks within the first months of life. A few months later, the parents noticed a centrally enlarging nodule within one of the sacral nevi, prompting referral to our hospital. Physical examination revealed a cerebriform fleshy tumor in the sacral region, along with multiple melanocytic nevi on the lower back and buttocks (Figure 1A). A biopsy from the congenital nevus component showed nevus cells with small, uniform nuclei between the collagen bundles. Ki-67 immunostaining showed a very low proliferation index, and the preferentially expressed antigen in melanoma (PRAME) immunohistochemistry was negative. The transition zone between the nevus and the tumor showed epithelioid melanocytes with irregular nuclei, a markedly increased Ki-67 index, and positive PRAME staining (Figure 2). Biopsy of the tumoral part showed a malignant spindle cell tumor of the skin, merging with superficial subepidermal aggregates of densely packed, round cells with hyperchromatic, irregular nuclei. Both components stained diffusely positive for S100. PRAME stained the nuclei of most round and spindle cell components. The round cells were also positive for SOX10, HMB45, and MART1, with a Ki-67 proliferation index of approximately 90%, while the spindle cell component demonstrated a lower index of around 30% (Figure 3). Breslow thickness was at least 10 mm. BRAF immunostaining was negative, and P16 demonstrated a mosaic expression pattern without loss. Desmin and MYOD1 were positive in some of the spindle cells, whereas myogenin was negative. Preoperative PET-CT and lymphoscintigraphy suggested inguinal lymph node involvement, with no evidence of distant metastases. Surgical excision was performed, but clear margins were not achieved. Histopathology of the excised tumor confirmed features consistent with melanoma, including areas of transition from CMN to melanoma. Lymph node biopsy confirmed metastatic spindle cell melanoma with PRAME positivity. Next-generation sequencing (NGS), performed using the Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific), identified pathogenic mutations: *BRAF* c.1781A>G (p.Asp594Gly, variant allele frequency [VAF] 37.1%) and *BCOR* c.4435_4436insTTGG

(p.Leu1480GlyfsTer11, VAF 42.0%). The patient was treated with combination immunotherapy: nivolumab (1 mg/kg) and ipilimumab (3 mg/kg). An initial response was observed; however, disease progression occurred during subsequent nivolumab monotherapy (3 mg/kg) (Figure 1B). Following progression on immunotherapy, tovorafenib – a pan-RAF inhibitor – was initiated under compassionate use. Tovorafenib was administered once weekly and was initially well tolerated. However, the tumor exhibited aggressive local behavior and continued to progress. The patient developed local bleeding, pulmonary metastases, and pelvic lymphadenopathy. Treatment was discontinued after eight doses due to disease progression and general deterioration. Supportive care was initiated, during which her appetite improved, serum albumin increased, and transfusion needs diminished. Despite stabilization of treatment-related toxicities, the melanoma progressed aggressively, and the patient passed away two months later.

Discussion

Melanoma arising in CMN represents a rare and biologically distinct subset of pediatric melanoma. Risk factors for melanoma development are multifactorial, including CMN size, location, and the presence of satellite lesions. In our patient, the "bathing trunk" distribution and the presence of numerous satellite nevi likely contributed to malignant transformation,[7] despite the CMN not meeting criteria for a giant nevus.[7,8]

Most melanomas associated with CMN harbor activating *NRAS* mutations, particularly in exon 3, which activate the MAPK pathway and confer sensitivity to MEK inhibitors. However, our patient's tumor was *NRAS*-negative – a feature shared with other aggressive pediatric melanomas.[6-8] These *NRAS*-wild-type tumors often exhibit highly malignant behavior and are associated with poor clinical outcomes. A limitation of our case is that the CMN was not sequenced separately. However, it is uncommon for *NRAS* mutations to be present in the nevus and absent in the associated melanoma, making this unlikely.

In our case, NGS identified a rare Class 3 *BRAF* mutation (c.1781A>G; p.Asp594Gly). Class 3 *BRAF* mutations differ markedly from the more common Class 1 (*e.g.*, V600E) and Class 2 mutations. Class 3 *BRAF* mutations are most commonly found at codons such as G466, D594, and G596. Tumors harboring these mutations frequently have concurrent alterations that maintain *RAS* activation, such as *RAS* mutations or *NF1* loss.[10,11]

Although Class 3 *BRAF* mutations are rare in melanoma, they occur more frequently in lung and colorectal cancers. In melanoma, they typically occur in older individuals and in chronically sun-damaged skin.[12] Melanomas harboring these mutations do not respond to standard RAF inhibitors, which

may even trigger paradoxical MAPK pathway activation. Therefore, MEK inhibitors or pan-RAF inhibitors like tovorafenib represent more rational alternatives, although pediatric-specific data are currently limited.[11,12]

In addition to the *BRAF* mutation, our patient's tumor harbored a *BCOR* frameshift mutation (p.Leu1480GlyfsTer11). Although the role of *BCOR* mutations in melanoma is poorly defined, they have been linked to aggressive pediatric malignancies and poorer clinical outcomes.[13] The concurrent presence of *BRAF* and *BCOR* mutations may reflect cooperative oncogenic effects, potentially accounting for the tumor's high proliferation index (Ki-67: 90%) and sarcomatoid histology. This co-mutation pattern warrants further investigation in pediatric melanocytic tumors.

Previous case series have demonstrated that melanoma arising in CMN is associated with a poorer prognosis compared to *de novo* melanoma. It is more likely to be diagnosed at an advanced stage, with greater Breslow thickness and higher rates of metastasis, leading to worse clinical outcomes and lower survival rates compared to melanomas not associated with CMN.[7-9,14] Predicting melanoma transformation in CMN remains a clinical challenge. MEK inhibitors have been shown to inhibit nevocyte viability and proliferation in *NRAS*-mutated CMN, both *in vitro* and *in vivo*.[9] A pivotal preclinical study demonstrated that topical MEK inhibition could prevent melanoma development in a murine model of giant CMN.[15] Although *NRAS* mutations were absent in our case, the MAPK pathway dependence of Class 3 *BRAF* mutations supports further exploration of MEK inhibitors in this molecular subset as well.[16]

The emergence of immune checkpoint inhibitors has revolutionized melanoma management in adults, and early pediatric data indicate similar promise.[17-20] Our patient initially responded to combination immunotherapy but progressed on monotherapy, emphasizing the importance of early escalation and the need for combination therapy in high-risk cases. Following immunotherapy failure, tovorafenib was introduced. This pan-RAF inhibitor has shown benefit in *BRAF*-driven pediatric low-grade gliomas and is under investigation for broader oncologic use.[21] In adults, immunotherapy is the first-line treatment even in the presence of a *BRAF* mutation. However, the optimal sequencing of therapies has not been adequately studied in the pediatric population. In our case, tumor progression despite tovorafenib may reflect intrinsic resistance of Class 3 *BRAF* mutations, the modifying influence of concurrent *BCOR* mutation,[10,20] or its introduction at a late stage, with multiple additional somatic mutations in different melanoma clones.

Histologically, the tumor exhibited a biphasic pattern, with both round cell and sarcomatoid components, and a markedly elevated Ki-67 index, characteristic of a high-grade malignancy. Interestingly, Baltres *et*

al.[17] described in 2019 a case morphologically similar to ours, involving the development of a bulky melanoma within a congenital nevus, where the melanoma also exhibited signs of dedifferentiation toward rhabdomyosarcoma markers. Similarly, in our case, some of the spindle cells showed positive staining for desmin and MYOD1, while myogenin was negative. Melanoma that underwent dedifferentiation, acquiring skeletal muscle markers, is an exceedingly rare phenomenon.[17] In their case, molecular testing revealed a *RAS* fusion: SASS6(e14)-RAF1(e8).

Conclusions

This case is notable for several unique features. First, the melanoma arose from a congenital nevus that, while not meeting criteria for a giant nevus, exhibited multiple satellite lesions – an established risk factor for malignant transformation. Second, histopathologic analysis revealed an aggressive sarcomatoid component composed of spindle-shaped cells, consistent with high-grade malignancy. Third, molecular analysis identified a rare class 3 *BRAF* mutation (c.1781A>G, p.Asp594Gly), along with a concurrent *BCOR* mutation, underscoring the genetic complexity of this case. Pediatric melanomas with such mutational profiles are exceedingly rare, and clinical guidance remains limited. Collectively, these distinctive clinical, histologic, and molecular features underscore the complexity of pediatric melanoma arising in CMN and highlight the urgent need for dedicated research and targeted therapies – particularly for pediatric patients with rare subtypes and atypical genetic profiles, including non-V600 *BRAF* mutations and concurrent alterations such as *BCOR*.

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Figure 1. A) Initial clinical presentation at 14 months of age showing a cerebriform, fleshy tumor arising from a congenital nevus in the sacral region, accompanied by multiple brown satellite nevi scattered across the lower back and buttocks. **B**) Disease progression demonstrated by enlargement of the primary tumor and the emergence of new lesions in the surrounding area.

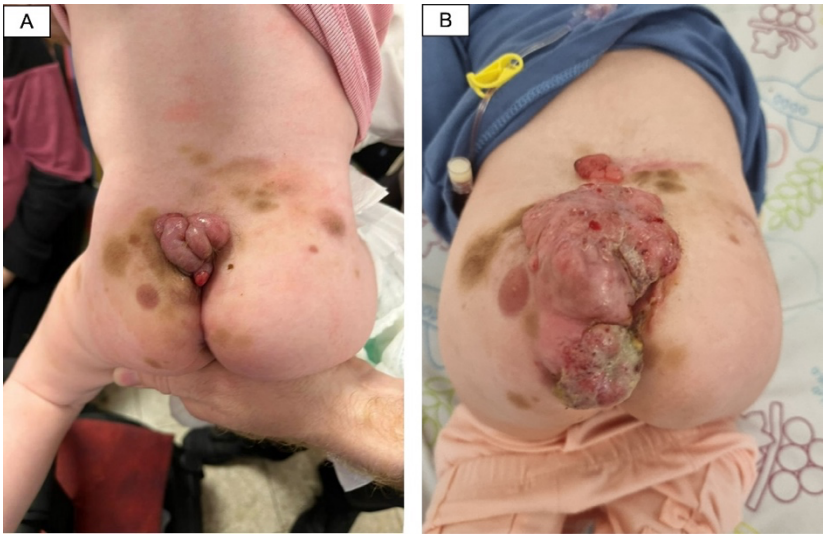

Figure 2. A) A biopsy from the congenital nevus part showing nevus cells with small, uniform nuclei and scant cytoplasm between the collagen bundles. **B**, **C**) Transition from the congenital nevus in A showing epithelioid melanocytes with irregular nuclei. **D**) Ki-67 immunostaining showing very low frequency in the congenital nevus (A). **E**) Markedly increased Ki-67 immunostaining frequency in the transition zone. **F**) Positive PRAME staining in the transition zone.

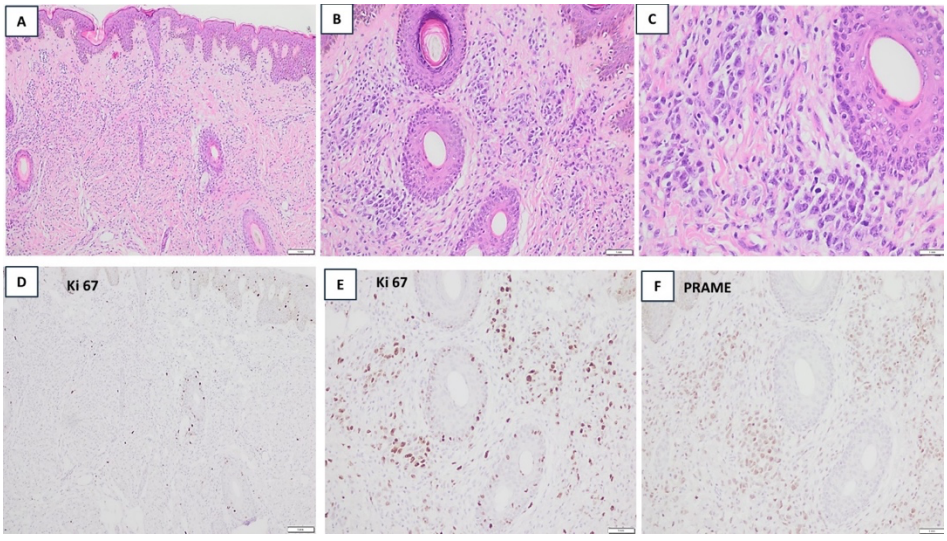

Figure 3. Histopathological features of the primary melanoma. **A**) low magnification showing clusters of crowded round cells with hyperchromatic nuclei in the upper dermis (left-hand side), and a dense infiltrate of spindle cells extending throughout the dermis (right-hand side). **B**) High magnification of the round-cell component, demonstrating hyperchromatic, irregular nuclei and high cellular density. **C**) The spindle-cell component is arranged in dense fascicles along the full thickness of the dermis. Immunohistochemistry: **D**) HMB45 stains the round cells and a small subset of the spindle cells. **E**) Diffuse PRAME positivity in both components. **F**) Relatively high KI67 positivity in both components.