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Case Report
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Pediatric Spitzoid Melanoma: A Case Report

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Abstract

Objective. To highlight the diagnostic and therapeutic challenges of Spitzoid melanoma in childhood, with a focus on its potential genetic predisposition. **Case Report.** A 7-year-old female patient presented with a growing nodular lesion on her upper leg. Excision was performed, and histopathological analysis confirmed a diagnosis of Spitzoid melanoma, classified as pT2a. Following a multidisciplinary review, wide local re-excision and sentinel lymph node biopsy (SLNB) were recommended. No residual tumor was found, and the SLNB was negative. A comprehensive diagnostic evaluation ruled out systemic disease, and no additional treatment was required. Germline genetic testing identified a pathogenic *CHEK2* variant (c.444+1G>A), prompting recommendations for genetic counseling and close follow-up. **Conclusion.** This case report contributes to the limited body of knowledge on pediatric Spitzoid melanomas and underscores the importance of genetic insights in guiding both diagnostic and treatment decisions. The detection of a *CHEK2* mutation underscores the importance of genetic profiling in family counseling.

Key Words: Melanoma ▪ Spitz Tumor ▪ Child, Genomics.

Introduction

Spitzoid melanoma is a rare pediatric neoplasm that presents a diagnostic challenge owing to its clinical and histopathological similarities with benign Spitz nevi and atypical Spitz tumors (1). While traditional histopathological assessment remains essential for diagnosis, advances in molecular genetics have provided valuable insights into identifying key mutations, such as *BRAF*, *NRAS*, and kinase fusions, which assist in tumor classification and risk stratification (2). Despite these advancements, the role of germline mutations, including Checkpoint kinase 2 (*CHEK2*) mutations, in pediatric Spitzoid melanoma remains unclear (3).

This case reveals a rare pathogenic *CHEK2* variant in a child with Spitzoid melanoma, highlighting the value of genetic profiling in guiding treatment and follow-up for this rare tumor.

Case Report

A 7-year-old female patient was referred to a pediatric hematologist after a 5 mm nodular lesion on her right upper leg was excised at a private clinic. Six months prior, a reddish-gray skin change, approximately 1 mm in size, was observed. A month before the excision, growth and color changes were observed, with the lesion almost tripling in volume and changing color to a brownish hue, accompanied by a central grayish area. The child had no complaints. The family history was negative for atypical moles, melanoma, or other malignancies.

The excised skin biopsy measured 5 × 4 × 1 mm and had a central grayish papule approximately 3 mm in diameter. Histopathological analysis revealed the accumulation of large melanocytes, primarily within the dermis, with some located in the epidermis. The cells exhibited an epithelioid

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appearance with a high nucleus-to-cytoplasm ratio, and their cytoplasm was abundant in pigment. Immunohistochemical staining revealed a medium-high Ki-67 proliferation index extending to the base of the lesion, along with a diffuse loss of p16 expression (Figure 1).

The finding was consistent with Spitzoid melanoma, exhibiting a Breslow depth of 1.77 mm and Clark level III. The tumor exhibited vertical growth and mitotic activity, with no signs of lymphatic invasion. Based on the pathological findings, it was classified as pT2a. The case was reviewed by a multidisciplinary team, which recommended re-excision of the lesion with wide margins, sentinel lymph node biopsy (SLNB), and genetic testing for cancer predisposition genes.

Re-excision was performed, and the specimen measured 4 × 2.8 ×1.2 cm. Serial sections showed no residual tumor. Hematoxylin and eosin (HE) staining and immunohistochemistry with S-100 and HMB-45 showed no tumor infiltration in the sentinel lymph node. Pathological review of the primary excision at another institution confirmed the diagnosis of Spitzoid melanoma. To assess potential metastases, comprehensive imaging studies, including abdominal, pelvic, and inguinal ultrasound, chest X-ray, chest computed tomography, and lymphoscintigraphy, were performed. All imaging studies showed no evidence of metastatic disease. As the malignancy was limited to the excised lesion, no additional treatment was indicated beyond the surgical excision. Genetic testing for hereditary cancer syndromes using next-generation sequencing (NGS) identified a heterozygous pathogenic variant in the *CHEK2* gene (c.444+1G>A). Variants of uncertain significance (VUS) were detected in the *PMS2*, *FLCN*, and *FANCI* genes. Genetic counseling was recommended. The father was unavailable for testing, and the mother tested negative for *CHEK2* mutations. The patient was followed up regularly and remained in remission three years after diagnosis.

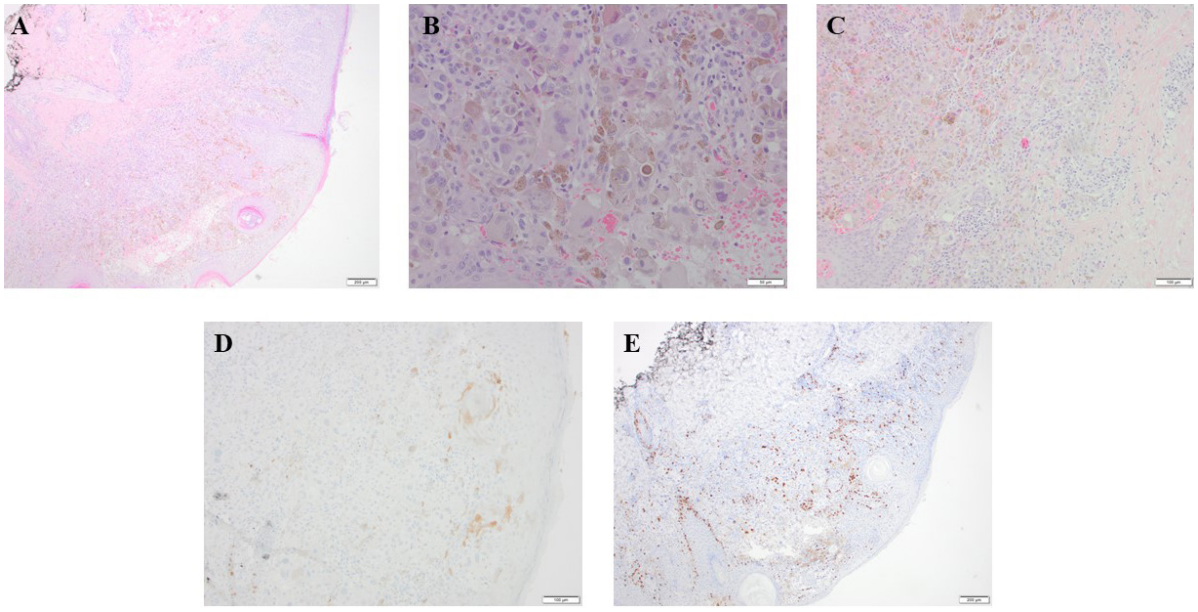

Figure 1. Spitzoid melanoma.
A. Predominantly dermal tumor composed of coalescing nests and sheets of large epithelioid melanocytes with pleomorphic nuclei and prominent nucleoli (H&E, 40×).
B. Large epithelioid melanocytes interspersed with lymphocytes (H&E, 200×).
C. Deep dermal component lacking melanocytic maturation, with tumor cells surrounded by lymphocytic infiltrate (H&E, 100×).
D. Loss of immunohistochemical p16 staining (IHC, p16, 100×).
E. Moderate-to-high Ki-67 expression in tumor cells (IHC, Ki-67, 100×).

Discussion

Spitz tumors, which encompass a wide range of melanocytic lesions from benign nevi to melanoma, have a specific histomorphology and distinct molecular pathways. Despite these features, standardized classification criteria for Spitz lesions are often lacking, leading to diagnostic uncertainty among pathologists and considerable variability in treatment recommendations (4). The 2023 World Health Organization classification of skin tumors sub-classifies Spitz tumors into three groups: Spitz nevi, Spitz melanocytoma (previously defined as atypical Spitz tumor), and Spitz melanoma (5). Unlike conventional nevi and melanomas, most Spitz melanomas are not clinically distinguishable from Spitz nevi. Spitz nevus typically presents in childhood or adolescence as a well-circumscribed, dome-shaped, pink to red papule or plaque, most commonly located on the face or lower extremities. It is composed of large epithelioid and/or spindle-shaped melanocytes (4).

There are no universally accepted criteria for distinguishing Spitz nevi from Spitz melanocytoma; however, several features have been proposed, including lesion size, degree of nuclear pleomorphism, depth, and predominance of large cell aggregates at the base of the lesion (6). Spitz melanomas often present as rapidly growing or color-changing nodules or polypoid lesions. They are commonly larger than Spitz nevi or Spitz melanocytoma, with diameters of 10 mm or more. While they can occur at any anatomical site, pediatric cases frequently present on the limbs. They are frequently amelanotic or exhibit ulcerated bleeding surfaces that mimic pyogenic granulomas. Notably, the ABCD criteria (asymmetry, border, color, and diameter) employed for assessing conventional melanoma are observed in fewer than 50% of Spitz melanomas, limiting their diagnostic reliability (7).

Merkel and colleagues introduced the term "Spitzoid melanoma of childhood" to distinguish them as a group of melanomas with a favorable prognosis. Based on their experience, only a small proportion of affected children develop lymph node or in-transit metastases, whereas distant metastases are exceptionally rare (8). Raghavan et al. proposed that the terms "Spitzoid melanoma" and "Spitz melanoma", although often used interchangeably, should be regarded as referring to distinct entities. Spitzoid melanoma generally refers to melanomas that exhibit characteristic morphology, comprising large epithelioid or spindle-shaped cells with abundant eosinophilic cytoplasm. In contrast to this purely morphology-based diagnosis, Spitz melanoma specifically refers to melanomas harboring genetic alterations characteristic of the Spitz lineage (2). Recent advancements in molecular biology have revolutionized our understanding of melanomagenesis. Up to 80% of Spitz neoplasms harbor oncogenic fusions involving either receptor tyrosine kinase genes (such as *ALK, FGFR1, MET, MERTK, NTRK1/2/3, RET,* and *ROS1*) or serine-threonine kinase genes (such as *BRAF, ERBB4, MAP3K3, MAP3K8,* and *PRKDC*). Importantly, these kinase fusions are mutually exclusive, and the fusion transcript is highly expressed in most cases (5). Therefore, an integrated approach combining morphological evaluation and genomic analysis is likely to remain the diagnostic standard for Spitz lesions.

Our patient presented with a reddish-gray, minimally pigmented limb lesion that was excised due to its growth and color change; however, the excision was inadequate. Immunohistopathology confirmed the diagnosis of Spitzoid melanoma. Given its rarity and the lack of advanced molecular techniques, a second opinion was sought, which confirmed the diagnosis. Wide re-excision and SLNB were performed. Although SLNB has been proposed for the management of these lesions, its role and prognostic value remain the subject of debate in pediatric practice (8). Cerrato et al. reported a 100% survival rate in pediatric SLNB-positive and regional lymph node-positive Spitzoid melanoma and melanocytoma (9). Batra proposed that most primary lesions can be managed with excision or re-excision with negative margins, followed by clinical follow-up and serial ultrasound monitoring of regional nodes (10). Since the lesion in our patient was localized and completely excised with clear margins, adjuvant therapy was not indicated.

In recent years, multiple germline pathogenic variants associated with an increased risk of skin malignancies have been identified, several of which are implicated in hereditary tumor predisposition syndromes. Spitz morphology in familial melanoma has been associated with germline variants in the *POT1*, *TERF2IP*, *ACD*, and *TERT* genes (11).

Genetic testing of our patient revealed a heterozygous pathogenic variant in the *CHEK2* gene (c.444+1G>A). *CHEK2* is a tumor suppressor gene that encodes the protein CHK2, a serine-threonine kinase, involved in the cellular DNA damage response. The association of germline *CHEK2* variants has been confirmed in breast, prostate, kidney, thyroid, and colon cancers (12). Several studies have reported an increased risk of melanoma in individuals with *CHEK2* mutations (13-15). Although their exact role remains unclear, they may contribute to the risk of Spitz melanoma due to their involvement in cell cycle regulation and tumorigenesis (15). The identification of the pathogenic *CHEK2* variant in our patient prompted counseling and facilitated a comprehensive follow-up.

This case underscores several important considerations. It is essential for clinicians to maintain a high level of suspicion and include melanoma in the differential diagnosis of atypical or evolving skin lesions in children. Moreover, amelanotic or hypopigmented melanomas can mimic a range of other conditions, causing diagnostic delays or inappropriate biopsy or excision techniques. While Spitzoid melanoma can occur at any anatomical site, pediatric cases frequently present on the limbs, necessitating vigilance when examining lesions in these areas (7). The diagnosis of Spitzoid melanoma presents significant challenges in terms of histopathology. If molecular techniques for analyzing tumor tissues are not available, a review at specialized centers is highly recommended. In the genomic era, germline testing, which identifies novel pathogenic variants, can serve as a valuable tool for managing and monitoring affected children.

Conclusion

This case underscores the diagnostic and therapeutic challenges associated with childhood Spitzoid lesions. The identification of a pathogenic *CHEK2* variant emphasizes the value of germline genetic testing in atypical cases and raises important questions about its role in melanocyte biology. Although SLNB and wide local excision remain the standard approaches, our case supports the need for individualized management and follow-up strategies.

What Is Already Known on This Topic:

Spitzoid melanoma is an extremely rare childhood malignancy that presents diagnostic challenges owing to its shared clinical and histopathological features with benign Spitz nevi and Spitz melanocytoma. Amelanotic melanoma and its hypopigmented variants further complicate clinical diagnosis. Clinicians screening for melanoma should maintain a high level of suspicion and include it in the differential diagnosis of red skin lesions. Recent advances in molecular techniques have significantly improved the diagnosis, classification, and understanding of the underlying mechanisms of skin tumors in children.

What This Study Adds:

This study highlights the importance of tumor genetic profiling in improving diagnostic accuracy. Germline genetic testing plays a crucial role in identifying factors that may be implicated in melanoma predisposition and assessing long-term cancer risk. The identification of a pathogenic CHEK2 variant contributes to the growing body of evidence supporting molecular analysis as a crucial tool for managing complex melanocytic lesions in children. Close interdisciplinary collaboration between pediatric oncologists, pathologists, dermatologists, and geneticists is essential for managing these patients.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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