Title: Metastatic Spitzoid Melanoma in a Child: Case Report

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Abstract:

Spitzoid melanoma is an extremely rare and aggressive melanocytic neoplasm in childhood, and is clinically and histopathologically difficult to differentiate from other Spitzoid lesions. We present the case of a 6-year-old girl diagnosed with BRAF V600E-mutated infantile Spitzoid melanoma, metastatic to regional lymph nodes. The patient was treated with pembrolizumab (anti-PD-1) and local cryosurgery for palliative purposes, with a good initial partial response. Subsequent disease progression prompted the indication of salvage targeted therapy. She remains under multidisciplinary follow-up, has well tolerated treatment, and has not experienced visceral progression to date.This case underscores the diagnostic complexity of Spitzoid melanocytic tumors in childhood and highlights the importance of integrating histological and molecular data to guide therapeutic decisions.

Introduction:

Spitzoid melanoma refers to melanomas that display spitzoid morphology but lack the molecular alterations characteristic of Spitz tumors. In the pediatric population, it represents a rare and difficult-to-diagnose entity, with significant overlap in clinical, histopathological, and molecular features with other Spitzoid lesions:Spitz nevus (benign), atypical Spitz tumor (AST, intermediate potential), Spitz melanoma (SM, malignant).(1-4) Clinically, pediatric Spitzoid melanomas often present as rapidly growing exophytic or ulcerated nodules, frequently located on the extremities. They frequently exhibit aggressive clinical behavior, including a high propensity for regional lymph node involvement. (1-4)

Case report:

A 6-year-old girl with no relevant medical history presented with a six-month history of a progressive, ulcerated lesion on the right medial malleolus. Physical examination revealed an ulcerated, exophytic tumor measuring approximately 40 × 39 mm at this location (Figure 1), accompanied by palpable right inguinal lymphadenopathy. A skin biopsy showed an ulcerated tumor composed of epithelioid and spindle-shaped cells with moderate nuclear pleomorphism, prominent nucleoli, and extensive eosinophilic cytoplasm. The cells were arranged in confluent nests without progressive maturation. Necrotic foci, atypical mitotic figures, deep mitoses, and a mitotic index of 7 mitoses/mm² were observed. The tumor infiltrated the entire dermis, reaching the hypodermis, with a Breslow thickness of at least 6 mm (Clark level V) (Figure 2). No vascular or perineural invasion was evident. Immunohistochemistry was positive for HMB45 and Melan-A, with preserved p16 expression (Figure 3). Ki-67 was positive in approximately 35% of tumor cells, with no apparent gradient. The findings were consistent with infiltrative Spitzoid melanoma.

A mutation in the BRAF gene in exon 15 (V600E/D) was detected by molecular biology. Imaging and biopsy documented right inguinal lymph node metastasis. Other visceral lesions were ruled out through complementary studies. The diagnosis was infantile Spitzoid melanoma, stage IIIB (T4bN1bM0). In conjunction with pediatric oncology, treatment with pembrolizumab (2 mg/kg of body weight, administered every 21 days) was initiated and the patient underwent two palliative cryosurgery sessions

with an initial partial response (Figure 4). However, the patient presented disease progression, so treatment was changed to targeted therapy with Dabrafenib/Trametinib; she currently remains under oncological and dermatological follow-up.

Discussion:

Histopathologically, Spitzoid melanomas are characterized by a proliferation of epithelioid and spindle-shaped melanocytes with moderate to severe nuclear pleomorphism, prominent nucleoli, increased mitotic activity, and deep dermal invasion (1,4). The presence of atypical ulceration and mitoses, as seen in this case, further supports a diagnosis at the malignant end of the Spitzoid spectrum. However, these features may overlap with those of AST or Spitz melanoma. (1,4) Therefore, no single histopathologic criterion is pathognomonic, and the diagnosis requires the integration of clinical, histologic, and molecular data. (1-2,4)

SOX10 and Melan-A positivity confirms melanocytic lineage, whereas the Ki-67 proliferation index provides an estimate of the tumor growth fraction; a high index (as in this case, ~35%) is more suggestive of malignancy but is not exclusive to melanoma. Expression of p16, encoded by CDKN2A, is often lost in Spitzoid melanomas, particularly those with CDKN2A deletions, but preserved expression does not exclude malignancy. (1,4) Therefore, while immunohistochemistry may support the diagnosis, it is not definitive in isolation.

Molecular analysis is essential. In Spitzoid melanomas, activating mutations in the MAPK pathway typical of conventional melanomas are identified, such as NRAS, MAP2K1/2, NF1, KIT or BRAF V600E, as in the case presented. On the other hand, Spitz melanoma, according to the current WHO definition, is characterized by the presence of genetic alterations associated with Spitz tumors, mainly kinase gene fusions (e.g., ALK, NTRK1, BRAF -not V600-, MAP3K8, ROS1, RET, MET) or mutations in HRAS. (5-7)

Regarding management, the first-line approach for metastatic Spitzoid melanoma in children is immunotherapy. (8) Targeted therapy with BRAF and MEK inhibitors represents a rational second-line

approach in pediatric melanoma with BRAF V600E mutation, particularly after progression on immunotherapy.(8) The decision to switch to targeted therapy in this case is in line with current recommendations for immunotherapy-refractory BRAF-mutant disease, especially given the lack of visceral progression and good patient tolerance.(8) Long-term follow-up is critical in pediatric Spitzoid melanoma due to the possibility of late recurrences and the evolving understanding of disease biology.(5,7) This case underscores the diagnostic complexity of Spitzoid melanocytic tumors in childhood and highlights the importance of integrating histological and molecular data to guide therapeutic decisions.

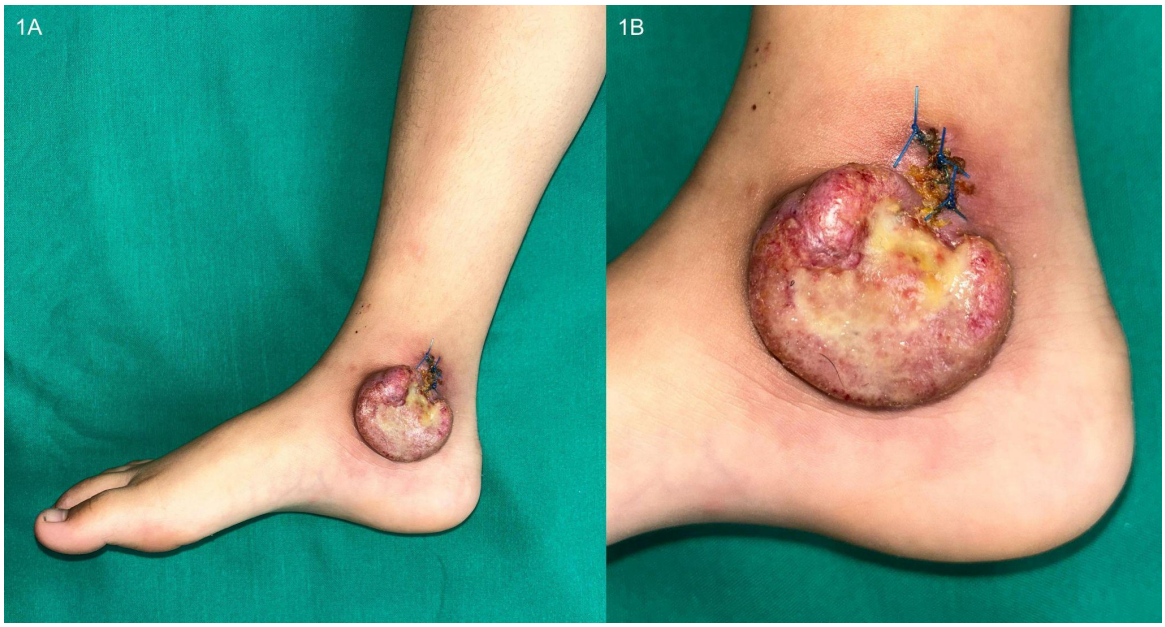
References:

1. Beydoun HM, Jeyakumar JE, Addo A, et al. A clinical, morphologic, and molecular comparison of bonafide Spitz melanomas and ASTs in the pediatric population. Am J Surg Pathol. 2025. doi:10.1097/PAS.0000000000002381.
2. Pampena R, Piccolo V, Muscianese M, et al. Melanoma in children: a systematic review and individual patient meta-analysis. J Eur Acad Dermatol Venereol. 2023;37(9):1758–76. doi:10.1111/jdv.19220.
3. McMullan P, Grant-Kels JM. Childhood and adolescent melanoma: an update. Clin Dermatol. 2025;43(1):16–23. doi:10.1016/j.clindermatol.2025.01.010.
4. Sondak VK, Messina JL. Melanoma in pediatric and young adult patients. Curr Oncol Rep. 2024;26(7):818–25. doi:10.1007/s11912-024-01542-5.
5. Kacar M, Yuan X, Pan H, et al. Influence of follow-up time on outcome of children and adolescents with atypical Spitz tumor/Spitz melanoma (AST/SM): results from the MACMEL registry. J Clin Oncol. 2023;41(Suppl 16):e21558. doi:10.1200/JCO.2023.41.16_suppl.e21558.
6. Pappo AS, McPherson V, Pan H, et al. A prospective, comprehensive registry that integrates the molecular analysis of pediatric and adolescent melanocytic lesions. Cancer. 2021;127(20):3825–31. doi:10.1002/cncr.33750.
7. Hatheway Marshall E, Alvarez G, Wang B, et al. Pediatric atypical melanocytic proliferations: single-site retrospective cohort assessment of treatment and long-term follow-up. Cancers (Basel). 2023;15(24):5804. doi:10.3390/cancers15245804.
8. Seth R, Agarwala SS, Messersmith H, et al. Systemic therapy for melanoma: ASCO guideline update. J Clin Oncol. 2023;41(30):4794–820. doi:10.1200/JCO.23.01136.

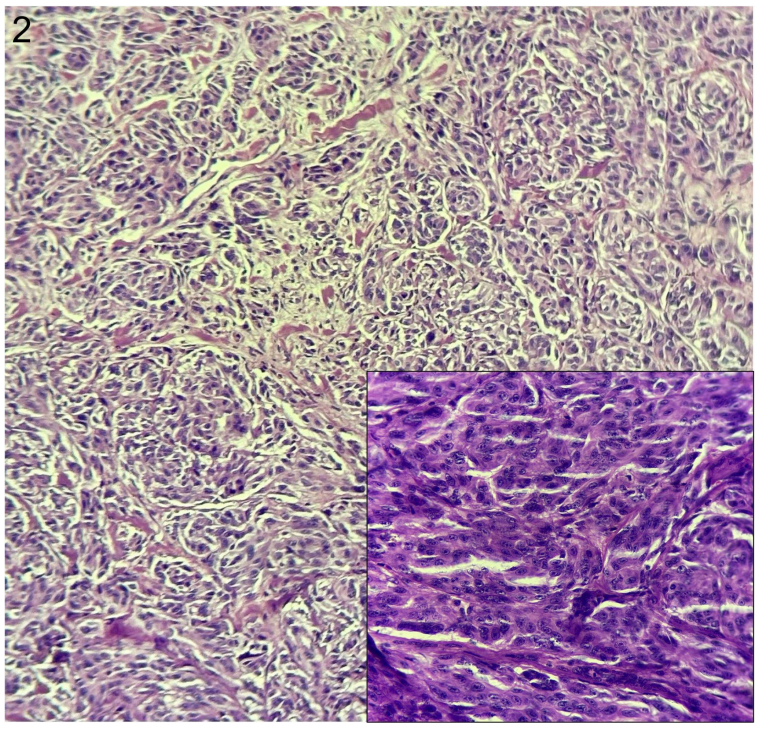
Figure legends

Figure 1a. In right medial malleolus ulcerated exophytic tumor measuring approximately 40 × 39 mm.

Figure 1b. Close-up.



Figures 2. H-E 20X (lower left box, 40X zoom).



Figures 3a, Melan A positive;*3b.* HMB 45 positive;*3 c.* P16 preserved.

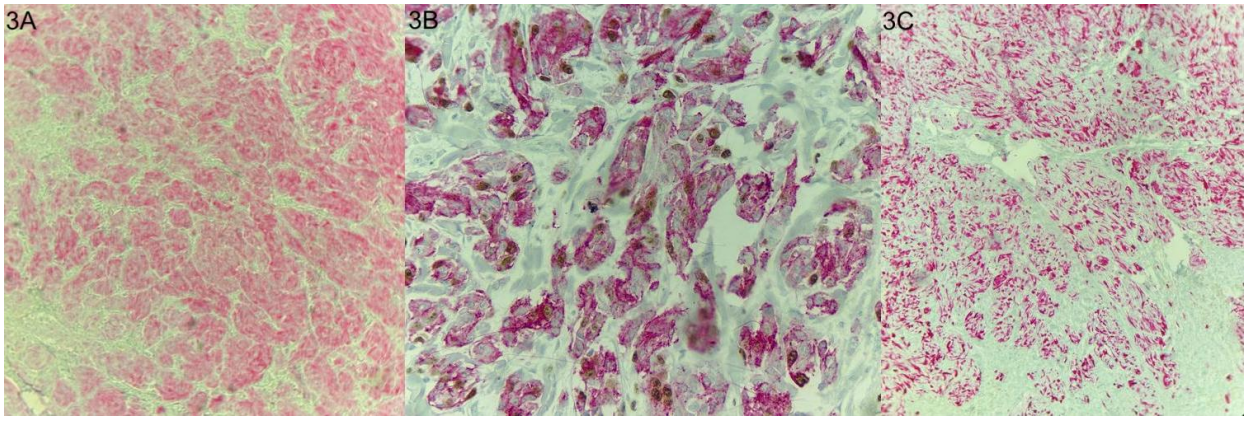


*Figure 4.*Outcome after palliative cryosurgery.