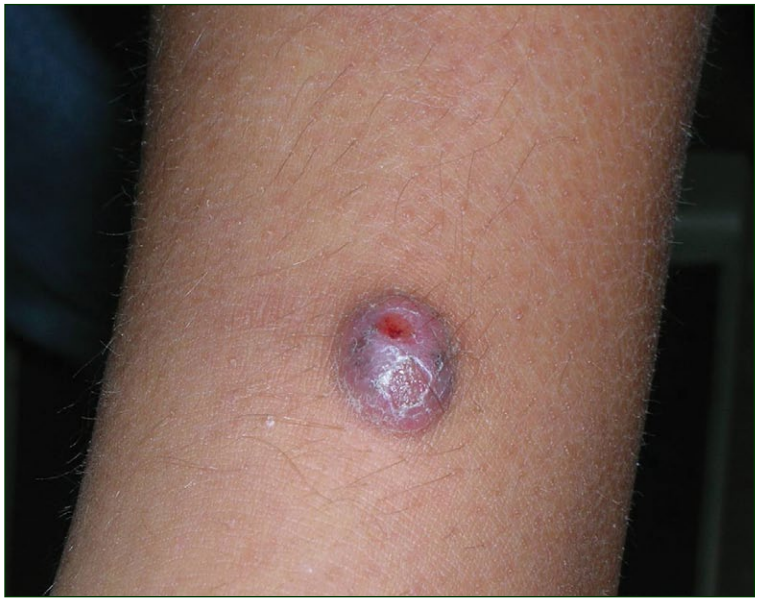
What Is Your Diagnosis?



A previously healthy 12-year-old white adolescent boy presented to the Vanderbilt University Dermatology Clinic, Nashville, Tennessee, with a 1-cm ulcerated nodule on the distal one-third of his left lower leg of 6 months' duration. The lesion was asymptomatic but had increased in size and had intermittently bled. His parents reported a considerable number of sunburns in his lifetime. His medical and family history was noncontributory. A shave biopsy was performed.

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The Diagnosis: Spitzoid Melanoma

Histopathology of the patient's ulcerated nodule (Figure 1) revealed an intradermal nodular proliferation of epithelioid cells with cytologic atypia (Figure 2). Tumor cells within the epidermis were appreciated and demonstrated pagetoid spread. Ulceration was present, but vascular or perineural invasion were not identified. Signs of regression, an associated melanocytic nevus, and microscopic satellite cells were absent. Mitotic figures, some atypical, were readily visible and appreciated near the base of the lesion (Figure 3). The tumor cells were strongly MART-1 (melanoma antigen recognized by T cells 1) positive. A diagnosis of a spitzoid melanoma (Clark level IV and 3.7-mm Breslow thickness) was rendered. The patient underwent local excision with 2-cm margins and sentinel lymph node mapping. Two excised lymph nodes demonstrated metastatic deposits with histologic features similar to the primary tumor. A left iliac nodal dissection and removal of an enlarged cervical lymph node were performed, but metastatic melanoma was not appreciated. Chest and abdominal computed tomography scans were clear. He was started on intravenous interferon alfa-2b (10 million IU/m^2 3 times weekly for 48 weeks), and he was free of disease after 5 years.

Spitzoid melanoma is a distinct subtype of melanoma resembling its benign counterpart, the Spitz nevus.[1] These tumors may appear pigmented but also may present as an amelanotic papule or nodule, mimicking an insect bite or pyogenic granuloma. Spitzoid melanomas typically are ABCD (asymmetry, border irregularity, color, diameter) negative, which makes clinical diagnosis problematic.[2]

Histologically, spitzoid melanomas often are difficult to distinguish from Spitz nevi. The former may demonstrate features of a Spitz nevus including epithelioid cytology, epidermal hyperplasia, and solitary or clustered eosinophilic globules (Kamino bodies). However, spitzoid melanomas are more likely to exhibit atypical mitoses, a mitotic rate of more than 2 mm^2, and mitoses within 0.25 mm of the lesion's base.[2,3] Additional features include size larger than 6 mm, asymmetry, poor circumscription, and lack of cell maturation with dermal descent.[4] A third category of lesions termed *atypical Spitz tumor* (AST) also has been described and a grading system for risk stratification has been proposed.[5,6] These neoplasms exhibit clinical and histologic features that fall between Spitz nevi and spitzoid melanomas. In an analysis of

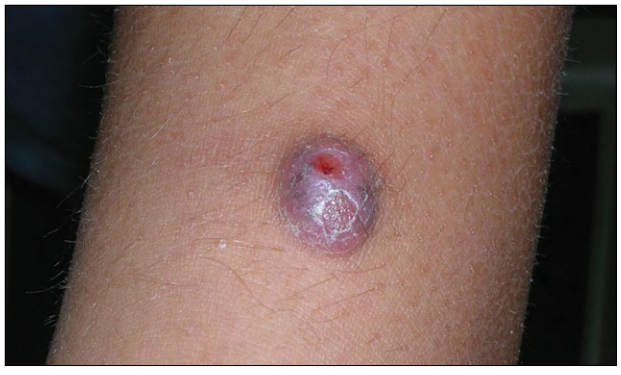

Figure 1. A dome-shaped erythematous nodule on the left lower leg with focal ulceration.

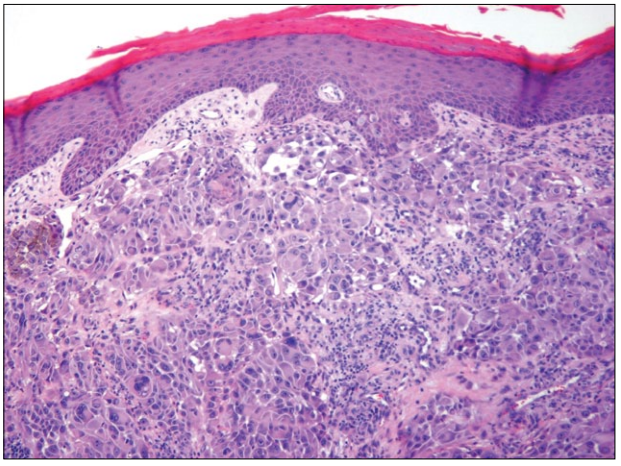

Figure 2. Intradermal aggregates of atypical epithelioid cells with appreciable cytologic atypia (H&E, original magnification ×100).

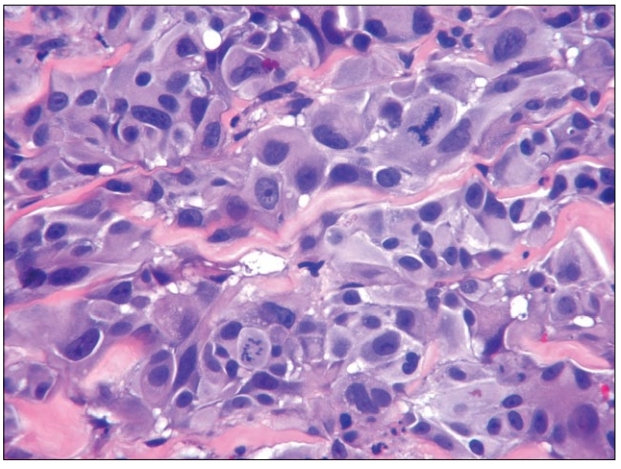

Figure 3. Epithelioid cells exhibited atypical mitotic figures (H&E, original magnification ×400).

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67 patients with ASTs, the median age was 23.7 years and 47% (27/57) of the patients undergoing sentinel lymph node biopsy (SLNB) demonstrated tumor deposits. Surprisingly, all of these patients were alive and free of disease at a median 43.8-month follow-up, which suggests that ASTs do not behave similar to conventional melanomas and exhibit a favorable prognosis.[6] Barnhill et al[7] proposed to abandon the appellation Spitz nevus in favor of terms such as *typical* and *atypical Spitz tumors* with recommendations for vigilant patient surveillance.

Immunohistochemistry and cytogenesis have been unhelpful, as both tumors typically are S-100 and HMB-45 (human melanoma black 45) positive, and staining for MART-1, cyclin D1, MIB-1 (mindbomb homolog 1), and bcl-2 (B-cell lymphoma 2) has been unable to distinguish Spitz nevi from spitzoid melanomas.[4] King et al[4] showed that 56% (15/27) of spitzoid melanomas but only 5% (3/58) of Spitz nevi were $CD99^+$ with the former exhibiting a diffuse staining pattern. Deletions on 6q and additions on 11p have been reported in spitzoid melanomas.[8,9] Lee et al[2] demonstrated that spitzoid melanomas lack the BRAF and N-*ras* mutations that have been found in 60% to 70% of melanomas, which suggests that spitzoid melanomas may develop via alterations in different genes and/or signaling pathways.

The diagnosis of childhood spitzoid melanoma imparts considerable clinical ramifications. Only 3% to 4% of melanomas arise in patients younger than 20 years and most are adolescents.[2,10] The prognosis is worse in adolescent patients versus their younger counterparts. In a retrospective review of 82 cases, patients 10 years and younger had an 89% (33/37) 5-year survival rate compared with 49% (22/45) in children aged 11 to 17 years, suggesting spitzoid melanomas may be biologically more aggressive in adolescents.[10]

Su et al[11] recommended that patients with atypical Spitz nevi thicker than 1 mm should undergo SLNB, as children with positive SLNBs appear to exhibit a higher incidence of nodal metastases and improved survival rates compared to adults.[12] Less than 5% of tumors 1 mm or thinner demonstrated a positive SLNB, whereas 30% to 50% of tumors that were more than 4-mm thick were positive.[11]

High-dose interferon therapy with subsequent maintenance therapy is recommended for patients with stage III melanoma, as it has been shown to prolong recurrence-free survival by 37% in adult patients. Therapeutic toxicities occur with similar frequency in pediatric and adult populations. Additional studies in children are needed before this therapy can be confidently administered to patients younger than 10 years.[10] Goh et al[3] described an 11-year-old prepubescent boy with spitzoid melanoma and regional inguinal metastases who was treated with 3-week cycles of vinblastine, dacarbazine, and cisplatin. The patient remained free of disease after 3 years of follow-up evaluations.[3]

Although malignant melanoma in children younger than 20 years is rare, melanoma in this age group is disproportionately of the spitzoid type. Thus distinguishing a spitzoid melanoma from its benign form, the Spitz nevus, is of great importance, especially in the pediatric population.

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