# Growing Pink Nodule on the Ankle

Timothy G. Webster, MD; Annyella Douglas, MD; Jason B. Lee, MD

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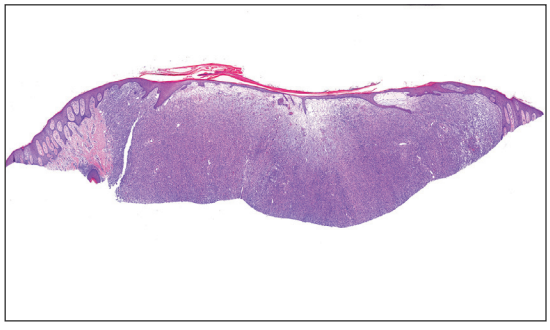

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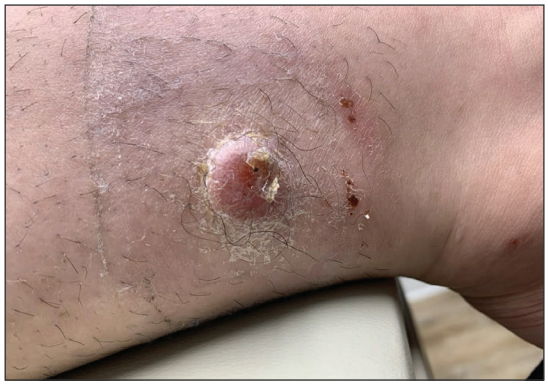

A 17-year-old girl presented to the dermatology department with a slow-growing lesion on the right lower leg that progressed in size over 1 year. The patient reported that the lesion occasionally bled but denied any other associated symptoms or a personal or family history of skin cancer. Physical examination revealed a solitary, well-circumscribed, circular, pink nodule on the right lateral upper ankle. Dermoscopy showed an amorphous mixture of pale and pink areas. A shave biopsy revealed a proliferation of epithelioid cells that diffusely stained positive for Factor XIIIa and anaplastic lymphoma kinase 1 and stained negatively for pancytokeratin, Melan A, CD34, ERG, CD31, SOX10, smooth muscle actin, desmin, and CD30. Next-generation sequencing revealed a vinculin and anaplastic lymphoma kinase gene fusion.

## THE BEST **DIAGNOSIS IS:**

a. atypical fibroxanthoma
c. cellular dermatofibroma
c. epithelioid fibrous histiocytoma
d. epithelioid sarcoma
e. intradermal Spitz nevus

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From the Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania.
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The eFigure is available in the Appendix online at www.mdedge.com/cutis.
Correspondence: Jason B. Lee, MD, 33 S 9th St, Ste 740, Philadelphia, PA 19107 (Jason.lee@jefferson.edu).
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# THE **DIAGNOSIS:** Epithelioid Fibrous Histiocytoma

In our patient, immunohistochemical stains for Factor XIIIa, CD68, and anaplastic lymphoma kinase (ALK) 1 confirmed the diagnosis of epithelioid fibrous histiocytoma (EFH). The location and relatively large size of the lesion led to a joint decision by the patient and physician to perform a complete excision, which was done with no complications.

Once considered a rare variant of dermatofibroma, EFH most commonly manifests as a solitary, vascular-appearing or flesh-colored papule or nodule on the legs. It often develops in the fifth decade of life with greater prevalence in men.[1-5] Our patient is one of the few known cases of EFH in children that have been reported in the literature.[3,6] Although EFH is benign, complete excision typically is performed due to the rarity of the lesion.[3]

The overexpression of *ALK* distinguishes EFH from other fibrohistiocytic lesions (Figure 1).[5] The most common fusion partners are sequestosome 1 and vinculin (*VCL*), which account for more than 70% of cases.[3,5,7] Interestingly, *VCL-ALK* fusions have been reported to occur in a subset of pediatric renal cell carcinomas and recently in an ovoid spindle cell neoplasm considered to be a low-grade sarcoma.[3,7-9] Further studies have identified less common fusion partners, including the dynactin subunit 1, ETS variant transcription factor 6, protein-tyrosine phosphatase, receptor-type, F polypeptide-interacting protein-binding protein 1, sperm antigen with calponin homology and coiled-coil domains 1, tropomyosin 3, protein kinase cAMP-dependent type II regulatory subunit alpha, melanophilin, and Echinoderm microtubule-associated protein-like 4 genes.[3,8]

In contrast to benign fibrous histiocytomas, EFHs primarily consist of epithelioid cells, have well-defined borders, exhibit prominent vascularity, usually are situated close to the epidermis, and lack multinucleated cells or histiocytes laden with lipids or hemosiderin.[2] The characteristic histopathologic finding is rounded or angulated epithelioid cells, with eosinophilic cytoplasm accounting for more than 50% of the tumor cell population.[1-3,5] The nuclei of the epithelioid cells are rounded and vesicular with small eosinophilic nucleoli and low mitotic activity. Common clinical features include an exophytic nodule with a classic epidermal collarette and an epidermis that exhibits variable degrees of hyperplasia.[1-3,5] Epithelioid fibrous histiocytomas often are confined to the superficial dermis and rarely extend to the subcutaneous layer. The stroma is collagenous with prominent vascularity, although older lesions can become more hyalinized and sclerotic.[3] Histopathologically, these tumors can be a diagnostic challenge, as they often are mistaken for other fibrohistiocytic or melanocytic lesions.

Atypical fibroxanthoma (AFX) manifests as a dome-shaped exophytic nodule that can rapidly grow to 1 to 2 cm. Historically, it was thought to be a pseudomalignancy, but most investigators consider it within the spectrum of pleomorphic dermal sarcoma and undifferentiated pleomorphic sarcoma. Atypical fibroxanthoma usually occurs on the head and neck in elderly patients with sun-damaged skin. Histopathologically, the neoplastic cells of AFX range from atypical spindle cells and pleomorphic round to polygonal epithelioid cells to large, irregularly shaped multinucleated cells, some with foamy cytoplasm (Figure 2). The atypical spindle cells stain diffusely positive for CD10 and vimentin, while small subpopulations stain positively for CD68 or CD163 and procollagen 1. Smooth muscle actin inconsistently stains the tumor, and when it does, the staining typically is faint and patchy. Atypical fibroxanthomas usually do not stain positively for melanocytic, skeletal muscle, or keratinocytic markers.

Cellular dermatofibroma typically manifests as small, dome-shaped papules on the arms and legs that normally range from a few millimeters to 1 cm but occasionally measure up to 2 cm. Histopathologically, there are

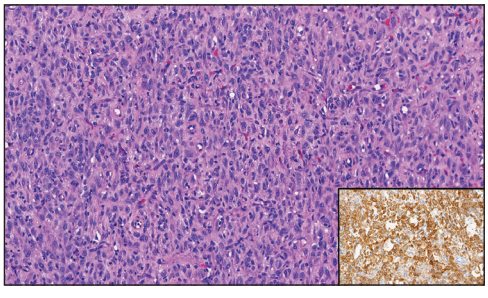

**FIGURE 1.** Oval to polygonal epithelioid cells with ample pink cytoplasm arranged in sheets, accompanied by small capillaries throughout the lesion. The inset shows diffuse staining for ALK1 (H&E, original magnification ×200).

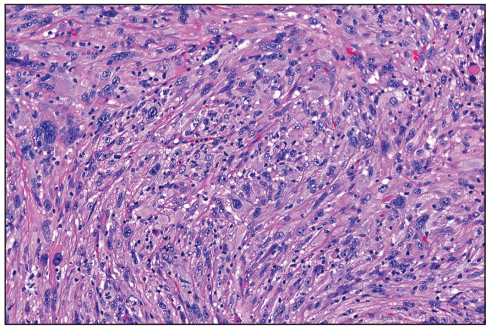

**FIGURE 2.** Atypical fibroxanthoma. Fascicles of large atypical spindle cells and atypical multinucleated epithelioid histiocytelike cells with scattered mitotic figures (H&E, original magnification ×200).

interweaving fascicles of spindle cells with hyperchromatic nuclei and peripheral splaying of the plump spindle cells that wrap around collagen bundles, known as collagen trapping (Figure 3). Unlike EFH, multinucleated cells and histiocytes with abundant lipids and hemosiderin often accompany the spindle cells in cellular dermatofibromas, which stain strongly positive for CD10 and vimentin, similar to AFX and EFH. The smooth muscle actin–staining pattern usually is faint and patchy, and in some cases, cellular dermatofibroma may not stain at all. Factor XIIIa and CD68 highlight the 2 populations of cells—fibroblasts and histiocytes—that make up the lesion.[4]

Epithelioid sarcoma comprises 2 types: distal (or conventional) type occurring on the distal arms and legs, particularly the hands and fingers of young adults, and proximal type occuring on the trunk and proximal extremities, including the upper arms and thighs.[10] Epithelioid sarcoma is a rare aggressive malignancy that usually manifests as a firm nodule, sometimes with ulceration depending on the size. Histopathologically, diffuse dermal proliferation of ovoid to polygonal epithelioid cells arranged in short fascicles and nodular aggregations is observed (Figure 4). Spindle cells may be observed at the periphery of the lesion. Areas of necrosis are a frequent finding and a helpful diagnostic clue. Nearly all cases stain positively for pancytokeratin, CAM5.2, epithelial membrane antigen, and vimentin, and approximately half stain positively for CD34; there are variable expressions of ERG and smooth muscle actin.[10] In most cases, epithelioid sarcoma does not stain positively for S100 or CD68. The majority (90%) of cases harbor a mutation in the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 gene, resulting in the loss of INI1 protein expression, which can be demonstrated by immunohistochemistry.[10] As the cytologic atypia usually is minimal, epitheliod sarcoma may be misdiagnosed as a necrotizing granuloma and benign fibrous lesions, particularly when superficial or small partial biopsies are performed.

Intradermal Spitz nevi can measure from a few millimeters to more than 2 cm and can range from pink to brown to black. The most common locations are the lower extremities as well as the head and neck. Histopathologically, intradermal Spitz nevi have nests of large epithelioid melanocytes with large nuclei and abundant cytoplasm (eFigure). Nuclear pseudoinclusions, which are cytoplasmic invaginations into the nucleus, are frequent. Unlike the other conditions in the differential, these entities stain positively for melanocytic markers—S100, SOX10, and Melan-A—but not CD68 or CD163.[11] A variety of kinase fusions are observed in Spitz nevi, including the *ALK* gene, neurotrophic tyrosine receptor kinase, ROS proto-oncogene 1, megakaryocyte-erythroid progenitor, and v-raf murine sarcoma viral oncogene homolog B1 genes.[12]

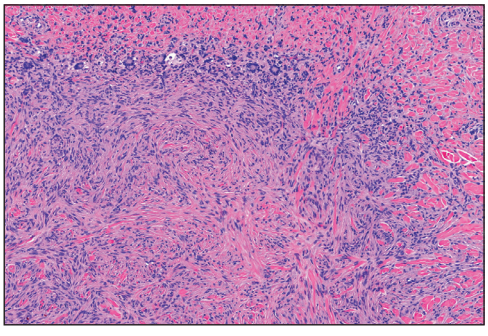

**FIGURE 3.** Dermatofibroma. Interweaving short fascicles of plump spindle cells with collagen trapping and hyperchromatic multinucleated cells at the periphery of the lesion (H&E, original magnification ×100).

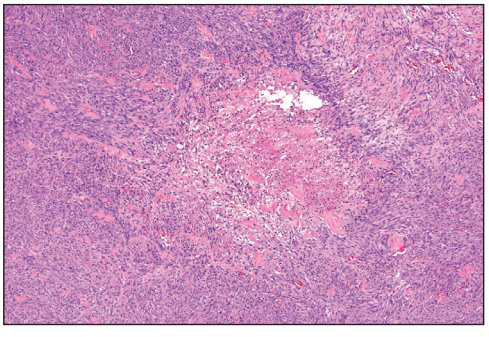

**FIGURE 4.** Epithelioid sarcoma. Diffuse proliferation of hyperchromatic plump epithelioid cells in dense fascicles with an area of necrosis (H&E, original magnification ×40).

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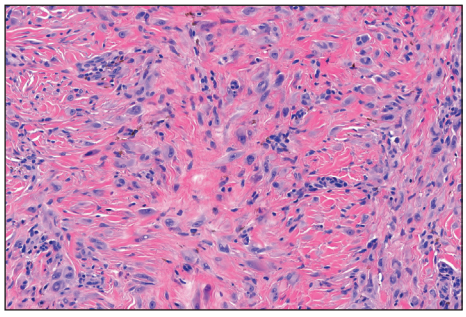
## APPENDIX



**eFIGURE.** Intradermal Spitz nevus. Large epithelioid melanocytes with abundant pink cytoplasm and large nucleus are splayed between collagen bundles in a slight fibrotic dermis accentuated by melanin granules (H&E, original magnification ×200).