

Epithelioid Sarcoma Resembling Benign Fibrous Histiocytoma

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Practice Points

- Epithelioid sarcoma should be considered in the clinical differential diagnosis of nonhealing recurrent lesions of the distal extremities in a young adult.
- Histological presentation of epithelioid sarcoma can mimic a number of benign granulomatous and fibrohistiocytic processes, including benign fibrous histiocytoma.
- Deeper biopsies may be needed to demonstrate the overtly malignant morphology characteristic of epithelioid sarcoma.
- Inactivation of SMARCB1/INI1 is a common molecular aberration identified in epithelioid sarcoma and can be demonstrated immunohistochemically by absence of nuclear staining in tumor cells.

Epithelioid sarcoma (ES) is a rare malignancy notorious for its tendency to histologically mimic granuloma annulare and other palisading granulomatous processes. We report a case of ES on the right hand of a 23-year-old man that histopathologically resembled a benign fibrous histiocytoma. Superficial portions of the tumor were well differentiated, exhibiting spindle and ovoid cells with scant cytoplasm that surrounded sclerotic collagen bundles. More obvious atypia including greater cellularity, nuclear pleomorphism, and mitotic activity were mostly confined to the deep-seated regions of the tumor. In addition to palisading granulomatous processes, ES can mimic benign fibrous histiocytoma, and the superficial portions of ES may appear deceptively benign.

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Epithelioid sarcoma (ES) is a rare malignant soft tissue neoplasm that is most often encountered on the distal extremities of young adults.¹ Epithelioid

sarcoma is notorious for its tendency to mimic palisading granulomatous processes such as granuloma annulare. We report a case of ES on the right hand of a 23-year-old man that resembled a benign fibrous histiocytoma (dermatofibroma) on incisional biopsy. The typical histopathologic features of ES were identified after amputation of the hand and evaluation of the deeper regions of the tumor. The tendency for ES to mimic granulomatous processes is a common diagnostic pitfall, but the potential for its close resemblance to benign fibrous histiocytoma is less recognized.

Case Report

A 23-year-old man presented with a nonhealing lesion on the right palm. His medical history was remarkable for a giant cell tumor of the tendon sheath involving the right fifth finger that had been treated via excision at an outside institution 2 years prior. Clinical examination revealed a 0.8×0.6-cm painful, firm, ulcerated dermal nodule with a hemorrhagic crust on the palmar surface of the right hand (Figure 1A). The clinical differential diagnosis included melanoma, traumatized verruca vulgaris, thrombosed pyogenic granuloma, and foreign body. A shave biopsy demonstrated verrucous epidermal hyperplasia, but the specimen did not include the dermis. Cultures of the lesion were positive for *Staphylococcus aureus*, and antibiotic therapy was initiated. In light of the clinical findings and the patient's history of a giant cell tumor, imaging studies were performed. Magnetic resonance angiography showed abnormal masslike infiltrative enhancement throughout

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the soft tissues surrounding the right fifth metacarpal bone. The differential included a recurrent giant cell tumor, fibromatosis, and other soft tissue neoplasms.

After several missed appointments and surgery cancellations, the patient returned 4 months later for an incisional biopsy. Physical examination revealed a persistent palmar ulcer that had grown to 1.4×1 cm in size, along with an indurated purple plaque wrapping around the ulnar aspect of the right hand (Figure 1B). The biopsy demonstrated a proliferation of spindled and ovoid cells with scant cytoplasm that surrounded sclerotic collagen bundles resembling a dermatofibroma (Figure 2A). Cytologic atypia and mitotic activity were absent (Figure 2B). Glass slides of the original biopsy, which ultimately led to the diagnosis of the giant cell tumor of the tendon sheath more than 2 years earlier, were obtained and showed similar features. The proliferating cells were strongly and diffusely immunoreactive for vimentin, CD34, and cancer antigen 125 (CA 125). Scattered tumor cells strongly expressed cytokeratins (CKs) AE1/AE3 and cell adhesion molecule 5.2 (Figure 3). Staining for CD99 and

epithelial membrane antigen was diffuse but weak. Factor XIIIa, S-100, CK7, smooth muscle actin, muscle-specific actin (HHF35), CD31, CD68, and B-cell lymphoma 2 were negative within the proliferating cells. Based on the clinical examination and results of the immunohistochemical staining, a diagnosis of ES was favored.

After a negative metastatic workup, amputation of the right hand was performed. The amputation specimen showed a tumor that extended through the entire hand with encasement of large vessels and tendons. Although the more superficial regions were cytologically bland, deep-seated regions of the tumor exhibited greater cellularity, nuclear pleomorphism, and mitotic activity (Figure 4). There was no bone involvement. Right axillary sentinel lymph nodes were negative for metastasis. Eighteen months later the patient developed chest and back pain with dyspnea. Thorascopic surgery was performed for a left pleural effusion and metastases to the left parietal pleura and adjacent soft tissue were identified. The patient was subsequently lost to follow-up.

Figure 1. A 0.8×0.6-cm ulcerated nodule on the hypothenar region of the right hand (A). Four months after initial presentation the nodule measured 1.4×1 cm (B).

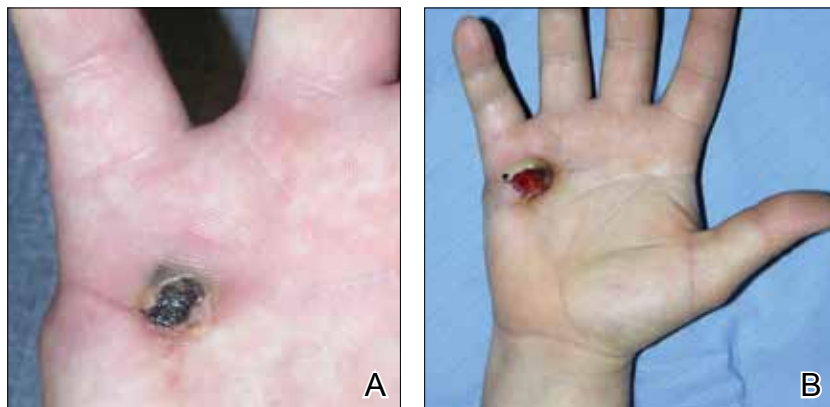
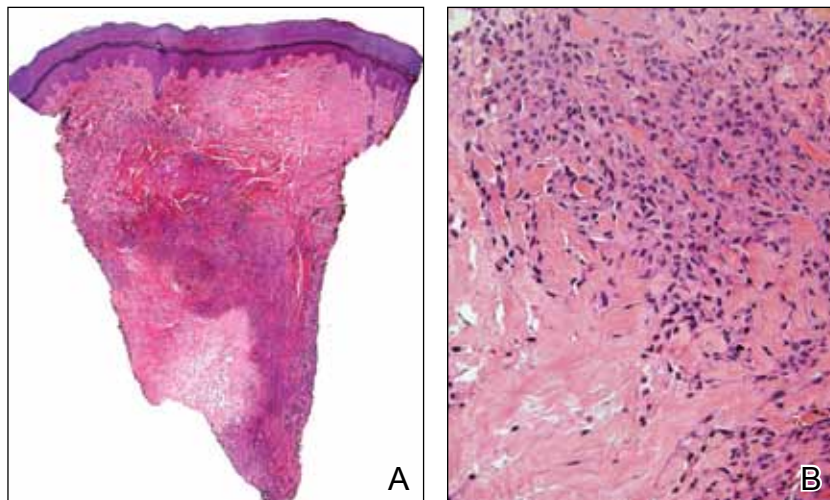


Figure 2. Low-power view of an incisional biopsy resembled a fibrohistiocytomalike neoplasm, as the tumor was composed of plump spindle cells that trapped sclerotic collagen bundles (A)(H&E, original magnification ×40). The tumor lacked significant cytologic atypia and mitotic figures were not seen (B)(H&E, original magnification ×200).



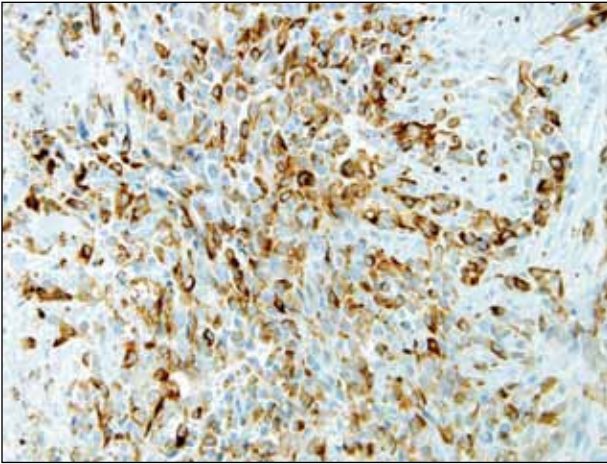


Figure 3. Tumor cells focally showed strong membranous staining for cytokeratin AE1/AE3 (original magnification $\times 400$).

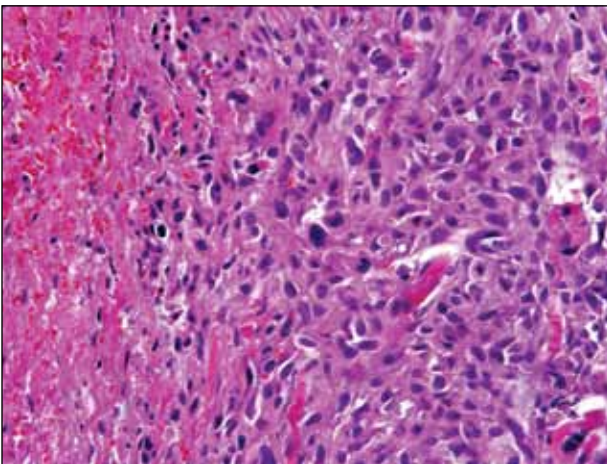


Figure 4. High-power view of the tumor from the amputation specimen showed sheets of epithelioid and polygonal cells displaying marked nuclear pleomorphism and scattered mitoses (H&E, original magnification $\times 400$).

Comment

First described by Enzinger¹ in 1970, ES is a rare malignant soft tissue neoplasm that most frequently arises on the hands, forearms, and pretibial soft tissues of young adults.¹⁻³ It is an aggressive tumor characterized by frequent recurrences and a high metastatic rate, with lung and regional lymph nodes being favored metastatic sites.¹⁻⁵ Periods of several months or even years often pass between the initial presentation and establishment of a correct diagnosis, as ES frequently is mistaken for other benign conditions. The tendency for ES to mimic granulomatous processes is a common diagnostic pitfall, but the potential for its close resemblance to benign fibrous histiocytoma is less recognized.^{6,7}

In his original series of 62 cases, Enzinger¹ noted that 17 patients were referred for treatment with a diagnosis of a benign fibrohistiocytic neoplasm, and other reports have described a resemblance to fibrous and fibrohistiocytic neoplasms.⁸⁻¹¹ Mirra et al¹⁰ designated these tumors as fibromalike variants of ES. Additional subtypes of ES have subsequently been recognized, including those described as angiomatoid or angiosarcomalike, reflecting the potential of ES to resemble vascular tumors.¹² A proximal type of ES also has been described. This lesion presents as a deep-seated tumor on the proximal limbs and is associated with more aggressive behavior. It lacks the granulomalike pattern and has more prominent epithelioid and rhabdoid histological presentation.¹³⁻¹⁵

Epithelioid sarcoma is a mesenchymal tumor that can display multidirectional differentiation that is primarily epithelial.¹⁶ The precise histogenesis of ES remains unclear, but studies have demonstrated a spectrum of differentiation that ranges from primitive myofibroblast or fibrohistiocytelike cells to those with well-developed epithelial properties.^{16,17} Epithelioid sarcoma characteristically coexpresses vimentin and low-molecular-weight CKs such as cell adhesion molecule 5.2. The tumor cells often are immunoreactive for epithelial membrane antigen and more than 50% of cases exhibit remarkable CD34 positivity.¹⁶ More recent studies have further refined the immunophenotype, demonstrating frequent expression of CK8 and CK19 but less commonly CK7, CK20, CK34 β E12, and CK5/6.¹⁸⁻²⁰ Additional studies reported that in 10 of 11 cases, ES was positive for CA 125 on immunohistochemical staining, and 3 of 5 patients also had elevated serum CA 125 levels.^{21,22} More recently, Hoshino et al²³ showed elevated serum CA 125 levels in 5 of 7 patients with ES. Cancer antigen 125 is a high-molecular-weight glycoprotein commonly used in the identification of epithelial ovarian carcinomas; however, it also has been described in a number of other neoplasms including carcinomas of the breast, lungs, and colon and lymphoma.²⁴⁻²⁷ Although it appears that the addition of CA 125 to a panel of other immunohistochemical stains may be helpful in differentiating ES from other soft tissue sarcomas and serum CA 125 levels may help determine tumor burden, currently the number of cases studied is too small to definitively make that conclusion.^{21,23} In our case, the tumor cells were strongly and diffusely positive for CA 125. Serum CA 125 levels were not available.

Cytogenetic studies have failed to identify a consistent chromosomal abnormality in ES.⁵ Some analyses performed by comparative genomic hybridization on isolated cases and small case series indicate that the most frequent alterations involve 8q, 18q11, and 22q11.^{13,28,29} The tumor suppressor

gene SMARCB1/INI1 (SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1/integrase interactor 1) has been mapped to 22q11, and ES commonly shows absence of nuclear staining for this protein, indicating inactivation.¹³⁻¹⁵

Conclusion

Benign fibrohistiocytic proliferations should be included in the differential of histological mimickers of ES. Deep biopsies are essential to differentiate these benign tumors from fibrous histiocytomalike or fibromalike lesions of ES because superficial portions of ES may be well differentiated.

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