Spindle cell tumors that make you say, “Oh $$&%!”
This lecture will focus on examples of cutaneous tumors that present particular diagnostic challenges because of certain challenging morphologic features.

Case 1: Angiomatoid fibrous histiocytoma (AFH)

Clinical Features
AFH is fibrohistiocytic tumor of intermediate malignancy. It typically presents in children and young adults as cutaneous/subcutaneous nodules, usually on the extremities. (That said, it may present at any age and in a variety of locations. Last year I made the diagnosis on the trunk of a 58-year-old man.) There may be systemic symptoms such as weight loss and night sweats. The tumor has a high rate of local recurrence (~20-40%) but metastasis is rare (<5%).

Microscopic features
Microscopically AFH has a fibrous pseudocapsule with lymphoid aggregates. Most typically, the tumor is composed of histiocytic cells with a sheet-like to swirling growth pattern. Evidence of intratumoral hemorrhage and pseudovascular spaces are usually present. The pseudovascular spaces are lined by compressed tumor cells rather than endothelium. With that in mind, there is considerable histologic variation in AFH. As illustrated with the case available to preview, some cases have significant cytologic atypia causing confusion with pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma). We have encountered cases with a reticulated to cord-like growth pattern as well as cases with numerous associated eosinophils, prompting consideration of the diagnosis of epithelioid hemangioma/angiolympoid hyperplasia with eosinophilia. Immunohistochemistry can be helpful but is largely supportive rather than definitively diagnostic. Roughly 50% of cases are positive for desmin, EMA, CD68, and/or CD99.

Cytogenetics
Cytogenetically AFH has one of three different recurring translocations: t(12;16)(q13;p11) resulting in a \( FUS/ATF1 \) fusion gene, t(12;22)(q13;q12) resulting in a \( EWSR1/ATF1 \) fusion, and t(2;22)(q33;q12) resulting in a \( EWSR1/CREB1 \) fusion. The last appears to be the most common translocation variant. Given the sometimes confusing morphologic pattern and inconsistent immunophenotype, FISH to detect evidence of a translocation has become invaluable in the diagnosis of this tumor. FISH using breakapart probes for either \( EWSR1 \) or \( FUS \) is positive in about 80% of cases. In difficult cases, we routinely perform FISH for EWS and reserve FISH for \( FUS \) in \( EWSR1 \) negative cases, as about 75% of AFH have a translocation involving \( EWSR1 \). It should be pointed out that in about 15-20% of AFH, FISH studies will be negative. This could be the result of a cryptic translocation not detectable by FISH or the tumor may harbor an as yet unidentified translocation.

Differential Diagnosis
The differential diagnosis of AFH is varied. In cases from adults the possibility of metastatic carcinoma or melanoma may be entertained, with the fibrous pseudocapsule and lymphoid aggregates being misinterpreted as a true lymph node. The
immunophenotype can be a diagnostic pitfall. Given the tendency for this tumor to arise in children, desmin positive cases, especially cases with pleomorphism, can be erroneously labeled as a rhabdomyosarcoma. AFH is negative for skeletal muscle specific markers such as myogenin or Myo-D1.

Vascular tumors are often considered in the differential diagnosis, owing to the presence of hemorrhage and the pseudovascular spaces. Rare cases of AFH may have prominent eosinophils prompting consideration of epithelioid hemangioma. The absence of immunoreactivity for endothelial markers helps differentiate AFH from vascular tumors.

In cases with significant pleomorphism like the case presented, the diagnostic pitfall is labeling the lesion a pleomorphic sarcoma (malignant fibrous histiocytoma). Keys to avoiding this pitfall include low power features of AFH: the fibrous pseudocapsule with lymphoid aggregates and circumscribed nature. At high power, there are typically admixed relatively bland tumor cells, and the mitotic rate is still typically relatively low despite the pleomorphism. Another pleomorphic tumor that could be considered in the differential diagnosis is pleomorphic hyalinizing angiectatic tumor of soft parts (PHAT). PHAT has pleomorphic cells and evidence of intratumoral hemorrhage with hemosiderin deposition and ectatic, hyalinized vessels. However, PHATs lack the pseudocapsule and most express CD34.

Finally, another entity that enters the differential diagnosis is largely due to nomenclature. There is a tendency to mistakenly interchange the terms angiomatoid and aneurysmal. Therefore some mistakenly label a dermatofibroma with prominent hemorrhage as an angiomatoid fibrous histiocytoma when in reality the proper term is aneurysmal dermatofibroma or dermatofibroma with aneurysmal change. The latter term is preferred as it better avoids potential confusion.

**Case 2: Epithelioid Sarcoma**

**Clinical features**

Epithelioid sarcoma usually presents in young adults, most commonly on the distal extremities, but epithelioid sarcoma can occur in any age and almost any location. I have personally seen cases presenting in children as young as three and adults as old as 80 years of age. Similarly, while most occur on the distal extremities, I have seen cases arise on the face, trunk or vulva. The clinical presentation is often as a nondescript subcutaneous mass, but ulceration is relatively common and should always be a warning sign for potential epithelioid sarcoma in a cutaneous soft tissue lesion.

Epithelioid sarcoma has a high rate of local recurrence, between 50-85% of patients and a metastatic rate of 30-50%, often with late metastases. Favored metastatic sites are the lung and regional lymph nodes.

**Microscopic features**

Microscopically, epithelioid sarcoma usually presents as nodules of epithelioid cells with densely eosinophilic cytoplasm that resemble histiocytes. The nodules can have a pseudogranulomatous pattern, especially in nodules that have central necrosis. The
tumor nuclei are enlarged but generally bland without prominent nucleoli. Occasional cases can have a predominantly or exclusively spindled morphology and are often embedded in a hyalinized stroma. This morphology can be extraordinarily deceptive. The spindled cells are often embedded within a hyalinized collagenous stroma. Mitotic figures are usually present but the mitotic rate is usually relatively low. They frequently hyalinized collagen and can resemble cellular fibrous histiocytoma as well as inflammatory processes such as granuloma annulare or necrobiosis lipoidica.

By immunohistochemistry, epithelioid is positive for cytokeratins and will be positive for antibodies AE1/3, CAM5.2, and CK7. They are negative for CK20, and most are negative for CK5/6. Epithelioid sarcoma is positive for EMA, vimentin, and approximately 50% are positive for CD34. ES is negative for CD31. It should be noted that epithelioid sarcoma may be positive for Factor XIIIa, a potential jingoistic pitfall in cytologically bland cases. More recently negativity for INI-1 has been demonstrated a useful finding in the diagnosis of epithelioid sarcoma. Non-neoplastic tissue is essentially always positive for this nuclear marker, as are most tumors in the differential diagnosis.

**Differential Diagnosis**

The differential diagnosis of epithelioid sarcoma is varied. In more epithelioid tumors, the differential diagnosis includes granulomatous disease such as infection, granuloma annulare and sarcoidosis. The presence of at least focal nuclear atypia and immunoreactivity for cytokeratin is helpful in allowing distinction.

Exclusively or largely spindled epithelioid sarcomas (the so-called fibroma-like epithelioid sarcoma) like the case presented are often deceptively bland appearing. The stromal collagen is hyalinized. This can cause diagnostic confusion with benign fibrous histiocytomas, interstitial granuloma annulare, fibroma of tendon sheath or nonspecific reactive fibroblastic proliferations. The absence of secondary elements such as foamy macrophages and siderophages and peripheral collagen trapping can help distinguish epithelioid sarcoma from benign fibrous histiocytoma. Furthermore there is usually at least focal hyperchromasia and atypia in epithelioid sarcoma which helps differentiate epithelioid sarcoma from all of these entities. Of course, immunoreactivity for cytokeratins is helpful. For this reason, we are in the practice of routinely immunostaining any unusual “fibroblastic” appearing lesion on the distal extremities, especially if the lesion is all suspected cellular fibrous histiocytomas on the distal extremities with pan-cytokeratin antibodies, particularly in younger patients.

Epithelioid hemangioendothelioma typically presents in adults but with a relatively nondescript clinical appearance, usually a skin-colored nodule that lacks the violaceous appearance of vascular tumors. A vascular lesion is suspected in only a minority of cases. Microscopically, epithelioid hemangioendothelioma is composed of cords to nests of epithelioid endothelial cells. Cells with intracytoplasmic vacuoles (“blister cells”) are typical, but may be inconspicuous. Classically, approximately 50% of epithelioid hemangioendotheliomas have a vasculocentric growth pattern with tumors cells filling the affected vessel and extending out in a centrifugal fashion. This vasculocentric pattern, however, is less frequently encountered in cutaneous tumors. The most
characteristic feature is the cord-like arrangement of the epithelioid endothelial cells that are embedded within a myxohyaline stroma. In some cases the cord-like morphology is difficult to appreciate causing potential confusion with epithelioid sarcoma. Epithelioid hemangioendothelioma is usually immunoreactive for both CD34 and CD31, and approximately 25% are immunoreactive for cytokeratin. The combination of cytokeratin and CD34 immunoreactivity can cause confusion with epithelioid sarcoma. Immunoreactivity for CD31 and retained INI-1 expression is helpful.

**Case 3: Cutaneous epithelioid angiomatous nodule**

**Clinical features**

This is a relatively new entity first described in 2004. Clinically it usually presents in middle-aged adults may present in a broad age range with cases presenting in childhood and elderly patients. The majority of cases are small (<1.0 cm) solitary lesions but occasional multiple or eruptive forms have been described. They are usually erythematous to violaceous. The location is varied, most have been described on the trunk but a significant subset has also been described on the extremities and the head and neck area.

**Microscopic features**

Microscopically, cutaneous epithelioid angiomatous nodule is a circumscribed tumor. Recognizable vascular channel formation is usually focal in nature. They are largely solid and composed of epithelial endothelial cells with abundant eosinophilic cytoplasm. Intracytoplasmic vacuoles are usually apparent. The nuclei do not show significant pleomorphism but they typically are somewhat enlarged with a conspicuous nucleolus. These are mitotically active tumors with a mitotic rate up to 5 mitotic figures per 10 high power fields, but atypical forms are not seen. There is a variable inflammatory infiltrate usually composed of lymphocytes and histiocytes associated with cutaneous epithelioid angiomatous nodule. Occasional cases may show a significant eosinophil component. Cutaneous epithelioid angiomatous nodule is a benign tumor and is unrelated to underlying immunosuppression. The treatment is variable. Cases have responded to simple excision as well as topical steroids. There have been no reported cases of local recurrence or metastasis.

**Differential Diagnosis**

The differential diagnosis of cutaneous epithelioid angiomatous nodule includes epithelial hemangioma (angiolymphoid hyperplasia with eosinophilia), and it has been suggested that cutaneous epithelioid angiomatous nodule may be related to epithelioid hemangioma. Epithelioid hemangioma usually presents in the head and neck area of young adults as solitary or locally multiple lesions. Microscopically, epithelioid hemangioma has more well-formed capillaries lined by epithelioid endothelial cells and is associated with lymphoid aggregates and numerous eosinophils. There is frequently a larger damaged vessel towards the central portion of epithelioid hemangioma suggesting that this may be a reactive process.
Because of the epithelioid nature of the endothelial cells, epithelioid hemangiendothelioma can also be considered in the differential diagnosis. Epithelioid hemangiendothelioma is discussed in detail above.

Epithelioid angiosarcoma could also be considered in the differential diagnosis of cutaneous epithelioid angiomatous nodule. Epithelioid angiosarcoma typically occurs in adults and may occur as a cutaneous lesion but it is more common as a deep soft tissue mass of the extremities. Microscopically, the growth pattern is variable from solid sheets to obvious vasoformative channels. The tumor cells have an epithelioid morphology but more prominent nuclear atypia, frequent mitotic figures and atypical mitotic figures. Epithelioid angiosarcoma is also frequently immunoreactive for cytokeratin, a potential diagnostic pitfall. Cytokeratin immunoreactivity has not been described in cutaneous epithelioid angiomatous nodule despite its epithelioid morphology.

Case 4: Angiosarcoma

Clinical features:
Cutaneous angiosarcoma most commonly arises on sun-damaged skin of the head and neck of elderly patients. Most cases present as erythematous to violaceous nodules, but occasional cases can clinically mimic other entities including non-vascular tumors.

Microscopic features
Most cases show complex vessels lined by atypical endothelial cells with an interanastomosing pattern. Rarely, angiosarcoma can be predominantly composed of fascicles of spindled cells with little evidence of vascular differentiation. The presence of atypical vessels at the periphery and, when present, intratumoral hemorrhage are clues to the diagnosis.

Differential Diagnosis
The lack of prominent vascular differentiation in this case can result in a differential diagnosis of sarcomatoid squamous cell carcinoma, spindle cell melanoma, atypical fibroxanthoma or leiomyosarcoma. Recognition of the atypical vessels at the periphery and immunostains for vascular markers helps distinguish this histologic variant of angiosarcoma from melanoma or spindled squamous cell carcinoma. The degree of cytologic atypia is greater than what is seen in Kaposi sarcoma and angiosarcoma is negative for HHV8 stains.

Selected References


