INTRODUCTION

Epithelioid sarcoma is a rare soft tissue sarcoma in young adults (20-39 year olds) involving the upper extremities 60% of the time. The name was given by Enzinger in 1970 to a group of soft tissue sarcomas that were confused with a variety of malignant and benign conditions; especially granulomatous process, synovial sarcoma and ulcerating squamous cell carcinoma. There is a “proximal type” variant first described in 1997 (see sidebar in Histology section).

This article will focus on conventional "distal" epithelioid sarcoma. Epithelioid sarcoma is a slow growing tumor with a high rate of recurrence and metastasis. Slow growth of the tumor, paucity of symptoms, benign appearance in early stage imaging studies, and indistinctive pathologic findings in some cases makes the diagnosis of epithelioid sarcoma challenging. The rarity of the disease also makes performing large controlled clinical trials to evaluate different treatment options almost impossible. This article reviews the epidemiology, clinical and pathological features, diagnosis, treatment and prognostic factors in patients with epithelioid sarcoma.

EPIDEMIOLOGY

In an analysis of a database on upper extremity sarcomas in the United States, the incidence of upper extremity epithelioid sarcoma was 0.1 cases per million per year. In a recent study it has been shown that the incidence has been increasing, with annual percentage change of 5.2% since 1973 and the incidence was reported as 0.4 case per million in 2005. It has been shown to be the second most common soft tissue sarcoma in the hand and the sixth most common soft tissue sarcoma in the upper extremity. This tumor is more common in males (1.8:1) and affects the young adult population. In a large retrospective study 74% of the patients presented between the ages of 10 and 39 and the average age of presentation was 27 years. Upper extremity sarcomas in general are more common in Caucasians but a review of tumors from different countries has shown no racial or geographical predisposition for epithelioid sarcoma. Although less common in females, epithelioid sarcoma has a more favorable prognosis in this population. The most common primary site for epithelioid sarcoma is distal upper extremities although cases of involvement of other parts of the body like vulva, penis and spine have been reported.

CLINICAL FEATURES

Epithelioid sarcoma most frequently affects hands and forearms followed by distal lower extremities and proximal upper extremities (Figure 1). Most tumors present as firm-to-hard palpable masses, either in the deep soft tissue or in the dermis. Often the superficial lesions will ulcerate, causing a mistaken diagnosis of a poorly healing traumatic wound or wart. Deep tumors may mimic ganglion cysts or be attached to tendons and be mistaken for giant cell tumors of tendon sheath. Pain or tenderness is present only in about 20% of the patients. About 13% of patients will present with multifocal tumors, and about 13% of patients will present with metastatic disease. Hand tumors can cause contractures or nerve compression symptoms including muscular weakness and numbness. In a retrospective study, the average duration of symptoms before initial surgical procedure was 29 months, which indicates the slow growth of the tumor.
Unlike most other sarcomas, epithelioid sarcoma has a tendency for lymph node metastasis. In a long term study, 45% of patients with epithelioid sarcoma developed metastatic disease, with the lung (51%), lymph nodes (34%), scalp (22%) being the most common sites. Other sarcomas that spread nodally include rhabomyosarcoma, clear cell sarcoma, synovial sarcoma, and vascular sarcomas.

**Radiographic Features**

No consistent findings can be seen in conventional roentgenograms. Soft tissue mass or swelling can be seen in some cases. Rarely, speckled patterns of calcification or ossification are seen. Epithelioid sarcoma rarely causes changes in the adjacent bone other than demineralization or cortical thinning. MRI is the diagnostic modality of choice for imaging prior to biopsy and pathologic diagnosis. Its role is primarily determining anatomic boundaries, since there are few findings specific to epithelioid sarcoma. MRI can help differentiate tumor recurrence from postoperative changes. In a small study, it was shown to be effective in differentiating recurrence from postoperative changes after multiple excisions. Data on PET CT are rare, but one study looked at 160 soft tissue sarcomas, of which 3 were epithelioid sarcomas. All three were PET positive.

**Diagnosis**

Like other soft tissue sarcomas, tissue biopsy is the diagnostic modality of choice. Due to inconsistency of pathologic features of epithelioid sarcoma, it is important that both the biopsy and interpretation of the microscopic specimen is done by an experienced musculoskeletal oncologist and pathologist, respectively. Genetic testing shows promise in differentiating different types of sarcomas including epithelioid sarcoma.

**Genetic Testing:** INI1 (also known as hSNF5 and SMARCB1) is a member of SWI/SNF multi subunit chromatin remodeling complex located on the long arm of chromosome 22 (22q11.2). This complex exposes the DNA to transcription factors. This gene acts as a tumor suppressor gene and its inactivation has been shown previously in some rhabdoid tumors. Recently, the loss of INI1 gene has been shown in more than 80% of patients with epithelioid sarcoma. Besides epithelioid sarcoma, loss of INI1 gene has been found in malignant rhabdoid tumor, malignant epithelioid schwannomas and myoepithelial carcinomas. Immunohistochemical staining of INI1 is available and can be used for the diagnosis of epithelioid sarcoma.
**Histopathology**

Epithelioid sarcoma mostly involves the subcutaneous tissue, tendons and fascia. Microscopic involvement of the skin and skeletal muscle has been seen in 24% and 28% of the cases respectively. This sarcoma has a tendency to grow along fascial planes, and invade large vessels and nerves.

The usual gross appearance of epithelioid sarcoma consists of one or more white nodules with infiltrating margins. The nodular nature is one of the most characteristic features of this disease.

Under the microscope, the tumor consists of epithelial-appearing (ovoid or polygonal) cells well blended with fusiform cells which are strongly eosinophilic with many containing intracytoplasmic vacuoles (Figure 2). There are no distinct sheets of polygonal cells vs spindle cells as seen in biphasic synovial sarcoma. Variants include fibroma-like (spindle cell dominant) and angiomatoid (angiosarcoma-like growth pattern with epithelioid cells surrounding a cyst).

The most common pattern seen is a "Pseudogranulomatous" proliferation of cells around an acellular, necrotic central zone (Figure 3. The central zone usually contains hyalinized collagen and necrotic debris. Calcification can be seen in necrotic areas in 19% of the cases. Multinuclear giant cells can be present in a small number of tumors.

**Proximal Type Variant:** In 1997, a "proximal type variant" of epithelioid sarcoma was described arising in the deep parts of the pelvis, perineum, and proximal extremities. It consists of large epithelioid carcinoma–like and/or rhabdoid cells and has a more aggressive clinical course compared to tumors located distally. This variant is also referred to as "large cell epithelioid sarcoma" due to presence of large rhabdoid cells.

**Immunohistochemistry:** Immunohistochemical studies have shown that vimentin reactivity is present in almost all cases. Pankeratin AE1/AE3 and epithelial membrane antigen were positive in 96% and 98% of the cases respectively. There is consistent staining for CA-125, and some have suggested using it as a serum marker to monitor for metastasis. S100 is typically negative (distinguishing it from malignant peripheral nerve sheath tumor), as are endothelial markers (distinguishing it from epithelioid angiosarcoma), and CK5/6 (distinguishing it from squamous cell carcinoma). CD34 is expressed in 50-60% of epithelioid sarcomas, but is negative in carcinomas, helping to distinguish the two. P63 is also a useful marker that is present in virtually all squamous cell carcinomas, but absent in epithelioid sarcomas.
**TREATMENT**

Wide surgical resection remains the most recommended treatment modality. Epithelioid sarcoma has recurrence rates of up to 77% after marginal resection in some long term studies. For this reason, most authors recommend wide resection or tumor bed resection despite the dysfunction and morbidity associated with it. However, epithelioid sarcoma has been noted to spread proximally in the same limb, distant to the original tumor (so-called "local metastasis"), leading some to consider less radical treatments for local control. Amputation can be considered if there are multiple recurrences or if there is not a significant loss of function (like a finger tip). However, it does not seem to help with "local metastasis" control.

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**Sentinel Node Biopsy:** Since epithelioid sarcoma can metastasize to the lymph nodes, some have proposed sentinel lymph node biopsy and regional lymph node dissection. Other tumors where sentinel node biopsy has shown to be beneficial include melanoma and breast cancer, but outcome literature for sarcomas is lacking. Further research into this topic is needed.

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**Role of Adjuvants**

The fact that epithelioid sarcoma is rare and slow growing makes it difficult to have long term follow-up to find significant difference between different adjuvant treatment methods.

- **Chemotherapy** (doxorubicin) has been used for multifocal, large (>5cm), or metastatic disease. It has not been shown to improve survivorship, but there are not large published trials.

- **Radiation therapy** is used in some institutions for primary and recurrent cases for limb salvage, with favorable results compared to amputation, but it has not shown to improve overall survivorship. The late effects (scarring, stiffness, and neuropathy) can be particularly debilitating in the hand.

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**PROGNOSIS**

Five year survival and ten year survival rate for patients with epithelioid sarcoma are approximately 50-70% and 42-55% respectively. Gender, site, age of diagnosis, tumor size and microscopic pathology have been shown to affect prognosis. Gender has been shown in multiple studies to be an important factor in prognosis with female patients showing a more favorable outcome. Proximal lesions have been shown to have worse outcomes compared to distal lesions. Tumors that presented at an earlier age had better outcome. Tumors more than 2 cm in diameter and tumors with necrosis and vascular invasion have been correlated with worse outcome. Mitotic index is a prognostic factor as well.

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**SUMMARY**

Epithelioid sarcoma is a rare sarcoma that affects young adults with an affinity to the distal upper extremity (hand and forearm). It mostly starts as a painless slow growing mass, but not uncommonly presents as a multifocal lesion. It has a high tendency for recurrence and spread along lymphatic channels. Biopsy is the diagnostic method of choice, with nodular, "pseudogranulomatous" formation with polygonal cells blended with spindle cells as the most common pattern seen microscopically. Loss of INI1 gene has been documented in majority of epithelioid sarcomas and may be used to confirm the diagnosis. Treatment primarily consists of wide resection. The role of adjuvants is debated. Male sex, tumor size more than 2 cm, proximal tumors and presence of vascular invasion in the microscopic specimen are correlated with worse clinical outcome.
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