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Case Report

Proximal-type epithelioid sarcoma: a report of two privileged site cases and a review of literature

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Abstract: Proximal-type epithelioid sarcomas are exceedingly rare but are characterized by high local recurrence and metastatic rates. As a consequence, patients suffer from a very poor long-term survival. We present one case of a 54-year-old man with proximal-type epithelioid sarcoma. To the best of our knowledge, this study is the first to report a case of proximal-type epithelioid sarcoma with both infraorbital and nasion masses. Another case of a 53-year-old woman with primary proximal-type epithelioid sarcoma on the right inguinal region experienced recurrence on the right vulva and bilateral inguinal and pelvic lymph node metastasis. Pathological findings revealed that both patients were cases of proximal-type epithelioid sarcoma. Despite surgical resection, patients with early tumor metastasis and large masses are associated with poor outcome of proximal-type sarcoma. The lack of directed therapies against epithelioid sarcoma emphasizes the need to identify the molecular causes of the disease.

Keywords: Proximal-type epithelioid sarcoma, both infraorbital and nasion proximal-type epithelioid sarcoma, inguinal region proximal-type epithelioid sarcoma

Introduction

In the 1930s, epithelioid sarcoma was mostly described as a variant of synovial sarcoma [1, 2]. In 1970, a mesenchymal malignancy was reported to be composed of neoplastic tissue that exhibited epithelioid cytomorphology and a predominantly epithelial phenotype; thus, epithelioid sarcoma was first established as a unique entity by Enzinger [3]. In 1997, Guillou [4] described a "proximal-type" variant of epithelioid sarcoma, with more aggressive and rhabdoid features and increased cellular atypia.

Epithelioid sarcomas are relatively infrequent, and they account for 0.6% to 1.0% of all soft-tissue sarcomas [5]. Epithelioid sarcomas usually occur in the distal extremities of young adults, with higher occurrence in men than in women [3]. This condition is one of the most common soft tissue sarcomas of the hand [6]. This cancer is also characterized by a deceptively benign presentation and slow growth at the primary site; however, this sarcoma is aggressive and ordinarily associated with very high local recurrence and metastatic rates; thus, patients suffer from a very poor long-term survival [6]. The overall 5-year survival rates are 32%-78% [5, 7]. The most recent World Health Organization (WHO) classification scheme subdivided epithelioid sarcomas into two subtypes, each with different histological, genetic, and clinical features (**Table 1**).

In this report, an epithelioid sarcoma of the both infraorbital and nasion regions was described for the first time. Another case was previously misdiagnosed as syringe carcinoma. After the patient suffered from recurrence, the case was diagnosed as inguinal region epithelioid sarcoma. A review of literature provides suggestions for the diagnosis and treatment of epithelioid sarcoma.

Case report

Case 1

A 54-year-old man presented with a painless infraorbital and nasion masses of approximately 6 years. Physical examination revealed a 3.0

Table 1. Epithelioid sarcoma subtypes based on their distinct clinical presentations and histological features

Subtype	Distal	Proximal
Histology	Cellular nodules of epithelioid and spindled tumor cells with central degeneration and a granulomatous appearance	Multinodular and sheet-like growth of large and sometimes pleomorphic epithelioid (carcinoma-like) cells with enlarged vesicular nuclei and prominent nucleoli
Location	Often located in the superficial soft tissues of the distal extremities	Arise in deep soft tissue, and most often affects truncal regions
Age (years)	10-40	20-65
Percentage of all epithelioid sarcoma cases	67%	33%
Prognosis	Favorable	Unfavorable

cm × 10.0 cm mass that was centralized within both infraorbital and nasion regions. The patient underwent surgical resection of the maxillofacial region.

The macroscopic appearance of the left infraorbital masses measured 3.5 cm × 2.0 cm × 1.0 cm, the right infraorbital masses measured 3.0 cm × 2.5 cm × 0.8 cm, and the nasion that measured 3.0 cm × 3.0 cm × 2.0 cm. Microscopically, the masses in the subcutaneous tissues of the multinodular foci of necrosis were surrounded with abundant cytoplasm, as well as pink epithelioid cells and spindle shaped cells (**Figure 1A**). The cells had mild atypia and visible nuclear division. The vascular center was noted in some areas of growth and the invading nerve, and the morphological findings indicated proximal epithelioid sarcoma.

Case 2

A 53-year-old woman presented with a right inguinal mass of approximately 9 years. Physical examination prompted a 1.0 cm × 2.0 cm block in the right inguinal close to the perineal tissue. The texture was hard, the boundary was unclear, and the degree of activity was poor. The patient underwent right inguinal tumor resection, but the pathological diagnosis is unclear. A tendency toward sebaceous gland carcinoma from poorly differentiated malignant tumors of origin epithelial carcinoma was noted. After a year, 1.0 cm × 2.0 cm masses were found again in the right vulva of the patient. The patient underwent right vulva tumor resection, and the pathological results of the primary occurrence and the recurrence showed the presence of proximal-type epithelioid cells. Three months after the patient felt discomfort and swelling in the right lower limb, the pelvic computed tomography (CT) scan indicated bilateral inguinal, pelvic lymph node metastasis. Unfortunately, the patient was lost to follow-up.

The results of macroscopic examination showed a tumor (1.3 cm × 1.0 cm) with pinkish-grey lobulated nodules. Microscopically, the primary tumor cells were spindle to oval in shape and contained abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, similar to rhabdoid cells (**Figure 1B**). In recurrences (**Figure 1C**), the tumor cell has poor adhesion, which is characterized by epithelioid cells, with oval nuclei and small distinct nucleoli, and visible local necrosis focus. In vascular tissue, lymphatic assessment shows the tumor thrombus. Immunohistochemically, the tumor was positive for AE1/AE3, EMA (**Figure 1D**), CD34 (**Figure 1E**), and CD68 (**Figure 1F**) but weakly positive for vimentin and negative for desmin. Pathological examination suggested a diagnosis of proximal epithelioid sarcoma.

Discussion

Epithelioid sarcomas rarely involve the head and neck region. Epithelioid sarcomas of the vulva mainly occur in middle-aged and young women, who clinically show slow growth of painless solitary nodules in the mons veneris, clitoris, labia, and Bartholin's gland. According to literature, the onset of symptoms to diagnosis has an average time of approximately a year and a half [8]. In early epithelioid sarcomas of the vulva, the symptoms are usually unnoticed; tumor growth is slow, and the disease is rare. Consequently, the condition is easily misdiagnosed as benign tumor and treatment is delayed.

For epithelioid sarcomas, surgical resection is the first choice. However, given its invasive nature, even when the cutting-edge operation was clean, the local recurrence rate is 65%-

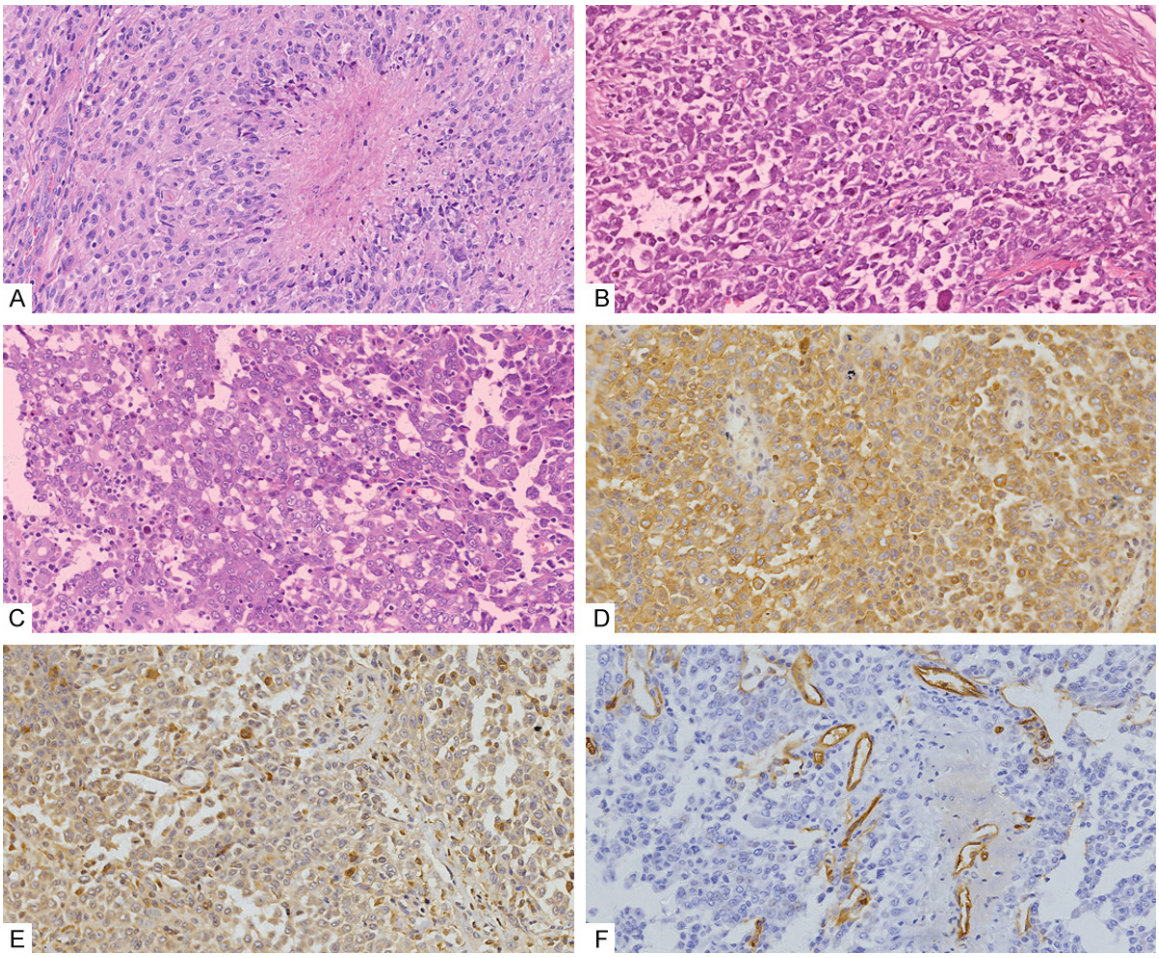

Figure 1. (A) Case 1. The masses in the subcutaneous tissues of the multinodular foci of necrosis were surrounded with abundant cytoplasm, pink epithelioid cells, and spindle-shaped cells. The cells have mild atypia. (B) Case 2, primary. The tumor cells were spindle to oval in shape and contained abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, similar to rhabdoid cells. (C) Case 2, recurrences. The tumor cells have poor adhesion, which is characterized by epithelioid cells with oval nuclei and small distinct nucleoli. (D-F) Immunohistochemistry of epithelioid sarcoma. The tumor cells were positively stained for (D) EMA and (E) CD68. (F) CD34 was positive in vascular endothelium. (A-F) 200 ×.

Table 2. Differential diagnosis of epithelioid sarcoma

Types of diseases	Immunohistochemical features
Benign tumor	Negative for CK and EMA
MM	Positive for HMB45, S100 proteins, and Melan-A
MPNST	Positive for S-100, NSE, and NF; negative for CK and EMA
LS	Positive for smooth muscle actins
RMS	Positive for desmin, myogenin, and MyoD1
AS	Positive for CD31, CD34, and D2-40
SS	Positive for epithelial immunophenotype (cytokeratin and EMA), Bcl-2, and neural markers; negative for CD34
MRT	Positive for SALL4; negative for ERG and CD34
Leiomyosarcoma	Negative for desmin and SMA

Benign tumor, including fibrous histiocytoma, nodular fasciitis, fibromatosis, and giant cell tumor of the tendon sheath; MM, malignant melanoma; MPNST, malignant peripheral nerve sheath tumor; LS, liposarcoma; RMS, rhabdomyosarcoma; AS, angiosarcoma; SS, synovial sarcoma; MRT, malignant rhabdoid tumors.

77%, and may even reach 85%; the recurrence is often multifocal, and occurs in a year after the initial treatment [8]. To date, in the recommended surgical procedure for local wide exci-

sion, the surgical resection margin is at least 2 cm. The metastasis rate of epithelioid sarcomas of vulva lymph nodes is 22%-45% [4, 8].

Epithelioid sarcomas have a wide range of microscopic characteristics and immunophenotypes; they can resemble numerous malignant neoplasms and non-neoplastic lesions, as well as benign skin and soft tissue. These sarcomas can be identified and diagnosed by immunohistochemistry. The differential diagnosis is listed in **Table 2**.

Epithelioid sarcomas occur in young individuals and are characterized by the loss of SMARCB1 (INI1, BAF47) nuclear expression and the expression of epithelial markers [9]. In infantile malignant rhabdoid tumors, the SMARCB1 gene is a tumor suppressor gene located at 22q11 and encodes for an invariant subunit of the SWI/SNF chromatin remodeling complex [10, 11]. The SWI/SNF complexes regulate cellular pathways by epigenetically affecting histone-DNA contacts and nucleosome remodeling [12, 13]. Notably, mutations in the SWI/SNF complex and other subunits, as well as in SMARCB1, such as BRM and the ATPase BRG1, have been identified in a large range of tumors, thereby suggesting that the SWI/SNF complexes function as a whole in tumor suppression [14, 15]. Recently published studies indicate that SWI/SNF-encoding genes have been linked to cancer, including ARID1A, PBRM1, and BRG1 [16, 17].

A recent study showed that SMARCB1 inactivation leads to hyperactivation of the ERBB1/EGFR and HGFR/MET pathways, thereby revealing new methods of treatment for epithelioid sarcoma [18]. Previous publications reported that EGFR is activated and expressed in epithelioid sarcoma patients and cell lines. EGFR activation induces epithelioid sarcoma cell proliferation, invasion, and motility, while increasing the level of MMP2, MMP9, and cyclin D1 expression. EGFR blocks significant cytostatic epithelioid sarcoma growth in vivo and inhibits these processes [19].

As a downstream node of the mTOR signaling pathway, the EGFR signaling pathway plays a major role in tumor progression and metastasis [20]. A recent study combined erlotinib/rapamycin to produce synergistic anti-epithelioid sarcoma effects and induce better tumor growth inhibition than single agent administration in vitro and in vivo [19]. Research indicated that the mTOR inhibitor induces the reactivation of AKT and ERK via a c-MET-dependent mechanism [21]. The combination of mTOR inhibitors and c-Met inhibitors provides a theoretical basis for the treatment of patients with epithelioid sarcoma [21]. The mechanism of AKT and ERK pathway activation in epithelioid sarcoma is based on hepatocyte growth factor (HGF)/c-MET autocrine signaling [21]. The overexpression of HGF and its receptor c-Met was observed in most epithelioid sarcoma cases [22]. HGF stimulated the phosphorylation of c-Met, which activates the downstream PI3K/AKT and MAPK/ERK signaling pathways [23, 24].

Thus, the dual targeting of AKT/mTOR and HGF/c-MET pathways may play an important role in the antitumor effects on epithelioid sarcoma cells where these pathways are activated. With recent research progress on the molecular mechanism of epithelioid sarcoma and improvements in the molecular targets of treatments, we can seek further medical treatment methods for epithelioid sarcoma, help patients reduce repeated surgical pain, and enhance the survival rate and quality of life of patients.

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Disclosure of conflict of interest

None.

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