Proximal-Type Epithelioid Sarcoma
-A Case Report and Review of the Literature

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Proximal-type epithelioid sarcoma is a rare, malignant soft-tissue tumor occurring in the proximal body sites of young to middle-aged adults and microscopically shows sheets of large polygonal cells with vesicular nuclei, prominent nucleoli and frequent rhabdoid features. Herein, we report a 27-year-old woman with proximal-type epithelioid sarcoma over the pubic area. The patient underwent wide excision, left inguinal lymph node dissection and split-thickness skin graft after biopsy proof. Pathological results showed an ill-defined nodule composed of large oval epithelioid cells in the dermis and subcutis. The dissected lymph nodes were free of tumor cells. We also review the literature regarding the clinical, pathologic and immunohistochemical features of proximal-type epithelioid sarcoma. Importantly, proximal-type epithelioid sarcoma has a much worse prognosis than the classical, distally located ones. (Dermatol Sinica 25: 274-278, 2007)

Key words: Epithelioid sarcoma, Rhabdoid feature

近端上皮樣肉瘤是一種少見的軟組織惡性腫瘤,主要發生於年輕至中年人的身體近端處。組織學上是以大的多角形細胞,伴隨空泡狀細胞核及顯著的核仁和常見的類橫紋形態。我們在此報告一位27歲女性於會陰部罹患近端上皮樣肉瘤,病患於切片診斷後即接受腫瘤廣泛性切除、左側腹股溝淋巴結切除及裂層皮膚移植。病理報告顯示在真皮及皮下有一界限不明的腫瘤,此腫瘤主要是由大型卵圓狀類上皮細胞所構成,淋巴結並沒有發現腫瘤細胞的存在。此外我們也回顧文獻上關於近端上皮樣肉瘤的臨床、病理、及免疫組織特性的報告中,重要的是近端上皮樣肉瘤比起傳統末端上皮樣肉瘤臨床的預後更差。(中華皮誌 25: 274-278, 2007)
INTRODUCTION

Epithelioid sarcoma, first described by Enzinger in 1970, is a rare soft-tissue malignant neoplasm appearing in the distal portions of the extremities of adolescents and young adults. Histologically, it consists of a subcutaneous or deeper nodular proliferation of round to plump, spindle-shaped cells with abundant eosinophilic cytoplasm palisading around areas of necrosis and simulating a granulomatous process. In 1997, Guillou et al. described a variant “proximal-type” epithelioid sarcoma, found mostly in the pelvic, perineal and genital areas of young to middle-aged adults and is characterized by a proliferation of oval to polygonal epithelioid cells with vesicular nuclei and prominent nucleoli. The rhabdoid feature was frequently found. We report a case of proximal-type epithelioid sarcoma in the pubic area and show the immunohistochemical data to emphasize the differential diagnosis of these unusual neoplasms.

CASE REPORT

A 27-year-old woman noticed a pin-head sized pimple over the pubic area one year before presentation to us. She visited the local medical clinic where folliculitis was diagnosed and topical medication was prescribed. However, the lesion became larger and larger, so she visited our hospital for further evaluation. One 1.5 x 1 cm in size, red-brown and elastic nodule on the pubic area was noted clinically (Fig. 1). Under the impression of ruptured epidermoid cyst, an excisional biopsy was performed. The specimen showed an ill-defined nodule composed of large, oval to polygonal epithelioid cells in the dermis and subcutis (Fig. 2A). The tumor cells possessed vesicular nuclei with prominent nucleoli and moderately copious amphophilic to eosinophilic cytoplasm (Fig. 2B). Small amount of spindle cells were interlacing with epithelioid cells. Occasionally, the proliferating cells showed...
rhabdoid features characterized by the presence of intracytoplasmic, paranuclear hyaline-like inclusions compressing and displacing the nucleus eccentrically (Fig. 2B arrow). Mitoses and atypical cells were noted. Focal necrosis, hemorrhage and inflammatory cell infiltration were also seen. The immunohistochemical studies showed the epithelioid cells exhibited a diffuse positivity for cytokeratin (AE1/AE3) (Fig. 3A), epithelial membrane antigens (EMA) (Fig. 3B) and vimentin (Fig. 3C). Focal positivity for smooth muscle actin was also noted. Tests for desmin, CD34, CD31, S-100, HMB-45, factor VIII, factor XIIIa, Fli-1, h-caldesmon and CD68 were all negative. According to the clinical presentation, histopathologic and immunohistochemical results, proximal-type epithelioid sarcoma was diagnosed. Further pelvic computerized tomography showed focal skin thickening at the midline of the pubic area. A small lymph node at the same level of left inguinal area was noted. Wide excision of the tumor with a 2 cm safe margin, left inguinal lymph node dissection and split-thickness skin graft were performed. The 2nd pathological report revealed residual epithelioid cells at the dermo-subcutaneous junction. Immunohistochemically, these cells were reactive to cytokeratin. The section margins were free. Two dissected lymph nodes were free of tumor. The patient didn’t receive any radiotherapy or chemotherapy. Long-term follow-up of the clinical condition was suggested.

DISCUSSION

Classical epithelioid sarcoma differs from proximal-type epithelioid sarcoma in terms of clinical presentation. Classical epithelioid sarcoma involves the superficial or deep soft tissues in the distal extremities, but proximal-type epithelioid sarcoma involves axial location, especially in the pelvis, the perineal area, the thigh, and the axilla.1

The histogenetic origin of epithelioid sarcoma is still not clear. Synovial origin has been favored.4 Another theory is a tumor of primitive mesenchymal cells with fibroblastic and histio-
cytic differentiation, or with histiocytic and synovial differentiation.

In 1997 Guillou et al. described 18 examples of proximal-type epithelioid sarcoma.2 Histologically, it shares with classical epithelioid sarcoma a predominant epithelioid cell population with marked cellular enlargement and vesicular nuclei, but differs mainly by exhibiting more rhabdoid features and by the less presence of granuloma-like pattern and the spindle-shaped cell component. The differences between

**Fig. 3**

Immunohistochemical staining of the proliferating epithelioid cells showed
(A) positive staining for cytokeratin. (Cytokeratin AE1/AE3, x100)
(B) positive staining for EMA. (EMA, x200)
(C) positive staining for vimentin. (Vimentin, x100)
proximal-type epithelioid sarcoma and classical epithelioid sarcoma were showed in Table 1.

The histologic term "rhabdoid" is used to describe large cells with vesicular nuclei, prominent nucleoli, and hyaline globular, paranuclear cytoplasmic inclusions often displacing the nuclei eccentrically inside a neoplastic proliferation. It has become clear that the rhabdoid phenotype is a nonspecific one and can be encountered in a large variety of nonrelated neoplasms, including melanoma, carcinoma, sarcoma and mesothelioma. Among the sarcomas, proximal-type epithelioid sarcoma is most likely to contain a large proportion of rhabdoid cells.

Tadashi et al. reported 20 cases with proximal-type epithelioid sarcoma. These tumors exhibit immunoreactivity for various markers: vimentin (100%); cytokeratin (100%); epithelial membrane antigen (85%); CD34 (45%); muscle markers, either desmin or α-smooth muscle actin (15%), and other markers such as S-100 protein, neurofilament, neuron-specific enolase, synaptophysin and CD 56 (60%).

The differential diagnosis of proximal-type epithelioid sarcoma comprises other epithelioid neoplasms involving the soft tissue, including classical epithelioid sarcoma, extrarenal rhabdoid tumor, synovial sarcoma, rhabdomyosarcoma, leiomyosarcoma, undifferentiated carcinoma, angiosarcoma, malignant peripheral nerve sheath tumor, cutaneous malignant melanoma, anaplastic large cell lymphoma, myoepithelioma and epithelioid cell histiocytoma.

Immunohistochemically both proximal-type epithelioid sarcoma and classical epithelioid sarcoma are distinguished from other sarcomas by the characteristic presence of cytokeratin AE1/AE3, vimentin, and epithelial membrane antigen with the absence of desmin, smooth muscle actin, factor VIII, factor XIIIa, S-100, HMB-45, CD31 and CD68. It must be stressed that CD34 may be positive in up to 50% of epithelioid sarcoma, thus vascular tumors must be excluded with at least one other vascular marker.

Contrasting with epithelioid sarcoma, so called extrarenal rhabdoid tumors are predominantly large neoplasms that occur preferentially in children younger than 10 years and show widespread anatomic distribution, including the nervous system, skin, visceral organs and soft tissues. Synovial sarcoma may overlap with some clinical aspects of proximal-type epithelioid sarcoma. Synovial sarcomas very frequently display cytokeratin, vimentin, and EMA immunoreactivity. The monophasic variety of synovial sarcoma is commonly composed of spindle cells, making it relatively distinguishable from proximal-type epithelioid sarcoma. Tumors with muscle differentiation, such as epithelioid rhabdomyosarcoma and leiomyosarcoma, are readily ruled out by the use of muscle-specific antibodies and eventually by the ultrastructure. Melanoma is easily discarded on the basis of S-100 and HMB-45 positivity. Malignant peripheral nerve sheath tumors.

Table. 1 The Differences Between Proximal-type Epithelioid Sarcoma and Classical Epithelioid Sarcoma

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<tr>
<th></th>
<th>Common sites</th>
<th>Age</th>
<th>Prognosis</th>
<th>Histopathology</th>
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<tbody>
<tr>
<td>PES</td>
<td>Proximal locations</td>
<td>Young to middle-aged adults</td>
<td>More aggressiveness</td>
<td>Frequent rhabdoid features</td>
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<td></td>
<td></td>
<td></td>
<td>Easy metastasis</td>
<td>Less granuloma-like pattern</td>
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<tr>
<td>CES</td>
<td>Distal extremities</td>
<td>Adolescents and young adults</td>
<td>Less aggressiveness</td>
<td>More spindle cell component</td>
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<td></td>
<td></td>
<td></td>
<td>Less mortality</td>
<td>Frequent granulomatous necrotizing appearances</td>
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PES, proximal-type epithelioid sarcoma
CES, classical epithelioid sarcoma
mor expresses S-100 positivity in 60% of cases and is cytokeratin and EMA negative. Epithelioid angiosarcoma may be cytokeratin positive, but it typically stains with endothelial marker (CD31, CD34, factor VIII). Finally, exclusion of undifferentiated carcinomas may be problematic as most of these lesions co-express EMA and cytokeratin. The occurrence of tumors in the subcutis or deep soft tissues without any connection with the overlying epidermis or cutaneous adnexa and the absence of histologic features of squamous or glandular differentiation favor the diagnosis of epithelioid sarcoma over undifferentiated carcinoma.

Since local recurrence is highly likely after simple excision, recommended treatment is wide excision or radical excision. In the series of Tadashi et al., thirteen (65%) of 20 patients with proximal-type epithelioid sarcoma developed local recurrence and 15 patients (75%) had metastases, primarily to the lymph node (80%), lung (47%), bone (27%), and skin (13%). At the follow-up of up to 19 years, 13 patients (65%) had died of the disease. Comparing to classical epithelioid sarcoma, 27–46% of the patients had died of disease. Proximally located epithelioid sarcomas behave more aggressively and metastasize earlier than conventional distally located tumors. A large tumor size (> 7.8 cm) and early metastasis were independently associated with a poor outcome. Radiotherapy treatment is effective as adjuvant treatment after primary surgery and as second treatment after surgery for local recurrence. Chemotherapy has not been proven to prolong survival, but novel agents and scheduling are under investigation.

Because of the indolent behavior, the high recurrent and metastatic rates of this tumor, long-term follow-up is indicated. Livi et al. recommend a follow-up every 3 months, combining clinical examination and chest X-ray for the first 3 years, then twice a year for another 2 years and then annually.

In conclusion, proximal-type epithelioid sarcoma is a rare, undifferentiated soft-tissue sarcoma with epithelioid features and a frequent rhabdoid phenotype. Proximal-type epithelioid sarcoma has a much worse prognosis than the classical, distally located epithelioid sarcoma.

REFERENCES