



Proximal-Type Epithelioid Sarcoma. A case Report of a Rare Tumor with Challenging Diagnosis and Review of the Literature

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Abstract

Proximal epithelioid sarcoma is a rare malignancy that develops from the proximal part of the body and occurs more commonly in young people. Because of its aggressive nature, high recurrence potential, and high ability to metastasize, it needs careful clinical long-term monitoring. This report intends to provide more insight to proximal epithelioid sarcoma due to its rarity. We report a case of a 31-year-old male, presented with proximal-type epithelioid sarcoma in his right ischio-rectal fossa and inguinal lymph nodes metastasis, confirmed by cytology sampling examination utilizing ultrasound fine-needle aspiration. We review the cytohistological presentation, molecular basis, immunochemistry, prognosis, and treatment of epithelioid sarcoma.

Keywords: Proximal epithelioid sarcoma; Fine needle aspiration; Cytopathology; recurrence; metastasis

ABBREVIATION

ES: Epithelioid sarcoma; **PES:** Proximal-type epithelioid sarcoma; **FNA:** Fine-needle aspiration; **IHC:** Immunohistochemistry

INTRODUCTION

Epithelioid sarcoma (ES) is a rare aggressive soft tissue sarcoma first described by Enzinger in 1970, which can be distal or proximal types [1]. The classic form (distal-type) of epithelioid sarcoma mainly occurs in teenagers and young adults. A rarer form, called large-cell (proximal-type) epithelioid sarcoma, tends to be more aggressive and mainly affects adults. The proximal subtype mostly arises from the proximal pelvis, limbs, and genital tract [2]. ES is a malignant mesenchymal neoplasm that exhibits epithelioid cytomorphology and a predominantly epithelial phenotype. The neoplastic cells in the proximal subtype tend to exhibit prominent malignant features including moderate nuclear atypia with prominent nucleoli and are associated with a poorer prognosis than the distal subtype [3]. The disease

normally presents as a painless, slow-growing, firm nodule deep in the soft tissues with a glistening and gray-tan appearance marked by superficial bleeding, necrosis, and ulcerations at the time of presentation [2]. ES can be diagnostically challenging and must be differentiated from various types of malignancy including non-mesenchymal tumors mainly carcinoma. In addition, it can be also misdiagnosed as a benign tumor. The survival rate of patients with ES is low, ranging from 25% to 70%, as reported by various studies [4]. Elsamna and colleagues analyzed 998 cases of ES and reported that the recurrence rate of ES was 63.4% and the metastasis rate was 40.3% [3]. Several predictive and prognostic factors were reported in the study of Elsamna et al including older age, necrosis, large size, and male sex. Patients were reported to be at a higher risk of death when they are older than 55 years. The diagnosis of metastatic disease has also doubled the mortality rate [3]. Here, we report a case of this uncommon tumor and we review the literature.

CASE PRESENTATION

A 31-years-old healthy man presented with a large 4.3 x 3.0 cm round soft tissue buttock mass at the right ischio-rectal fossa. He discovered the mass during workup as he felt discomfort at the sitting position, but did not seek any medical attention for one month until he noted progressive enlargement of the mass. Patient reported that the mass was associated with non-healing skin ulceration. Physical examination showed right inguinal lymphadenopathy in addition to the right buttock mass. Patient gave no significant prior medical history. Imaging studies showed multinodular appearance and hyperintensity relative to muscle on T2-weighted magnetic resonance imaging (MRI). Gadolinium-enhanced T1-weighted MRI image with fat suppression showed inhomogeneous enhancement. Soft tissue sarcoma was suspected and tissue sampling diagnosis was recommended. Ultrasound-guided fine needle aspiration (FNA) was performed

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and adequate cytology sample with sufficient cellblock material was obtained. The cytomorphologic examination showed a high grade malignant neoplasm with epithelioid features and extensive necrosis. The tumor consisted of epithelial-appearing ovoid and polygonal cells well blended with strongly eosinophilic fusiform cells occasionally containing intracytoplasmic vacuoles (**Figure 1A**). There were no distinct sheets of polygonal cells admixed with spindle cells as seen in biphasic synovial sarcoma. Pseudogranulomatous proliferation of cells around an acellular necrotic central zone was strongly noted (**Figure 1B&C**). Immunohistochemistry studies were performed on cellblock preparation and showed strong positive for Vimentin (**Figure 1D**), HMW-CK34, pancytokeratin AE1/AE3 (**Figure 1E**), EMA (**Figure 1F**), and focally for CD34. The tumor cells were negative for S-100, P63, synaptophysin, chromogranin, desmin, and Myogenin. The tumor cells showed high proliferation with > 40% nuclear staining with Ki-67. The cytomorphology together with immunohistochemistry profile was supportive of the diagnosis of proximal type epithelioid sarcoma. FNA of an enlarged lymph node at the right inguinal region was performed, which showed malignant cells similar to that seen in the buttock sample, consistent with metastatic epithelioid sarcoma. Right inguinal lymph node dissection was performed and 3 lymph nodes out of 12 were positive for metastasis. Imaging body scanning survey showed no evidence of metastasis at any other sites.

The buttock mass was surgically excised with adequate safe margins and patient received postoperative chemotherapy and radiation treatment. Newer treatment approaches such as the recently FDA approved Tazemetostat were not available at the time of presentation of our case. Patient was followed for two years with no evidence of recurrence or metastasis then was lost to follow up.

DISCUSSION

Epithelioid sarcoma (ES) is a rare, slow-growing type of soft tissue sarcoma. Typically, epithelioid sarcoma starts as a small firm growth or lump that's painless. Proximal-type epithelioid sarcoma (PES) is a rare variant of ES presenting in either a proximal lower extremity or axial location. PES affect the chest wall, inguinal area, thigh, and perineum in most cases. This rare neoplasm is often mistaken for benign lesions, resulting in delayed diagnosis and treatment. The differential diagnosis of PES including angiosarcoma, epithelioid leiomyosarcoma, epithelioid malignant peripheral nerve sheath tumor, metastatic carcinoma, epithelioid hemangioendothelioma, synovial sarcoma, rhabdomyosarcoma, and clear cell sarcoma [5]. Benign conditions such as granuloma annulare, giant cell tumors of the tendon sheath, benign fibrous histiocytoma, or necrotizing granulomas should also be considered. Immunohistochemistry studies (IHC) are essential to make the definitive diagnosis of these tumors [6]. PES should also be differentiated from a leishmaniasis-related ulcerated lesion with infiltrated edges in a leishmaniasis-endemic region [7]. PES is normally multinodular, with central necrosis and degeneration when examined under the microscope. A characteristic intense acidophilia can be seen with hematoxylin-eosin stained sections. In some cases, the nodules are well-circumscribed, and in others, they may be fused into irregular lobulated cellular masses. Cells can range in size from a plum spindle to large round cells, or they can be fused to form irregular lobulated cellular masses [4].

ES is considered a tumor of uncertain differentiation. Structural and immunohistochemical studies suggest a multidirectional differentiation, including epithelial, histiocytic, fibroblastic, myofibroblastic, endothelial and perineural origin.

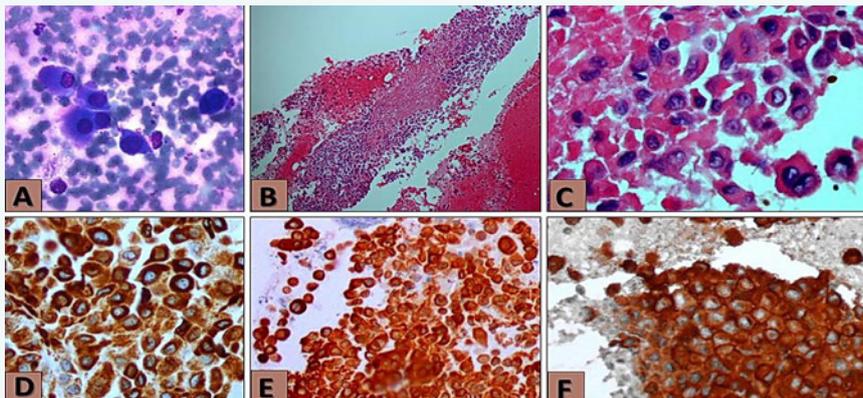


Figure 1 Cytomorphology and immunohistochemistry profile of the buttock mass

Figure 1A: The tumor consisted of epithelial-appearing ovoid and polygonal cells well blended with fusiform cells (Cytology smear DQ stain X 60 magnification)

Figure 1 B: Low power view of pseudogranulomatous proliferation of cells around an acellular, necrotic central zone (Cellblock H&E stain X20 magnification)

Figure 1 C: High power view showing proliferation of epithelioid cells with characteristic intense acidophilia around an area of necrosis (Cellblock H&E X60)

Figure 1D: Tumor cells positive for Vimentin

Figure 1E: Tumor cells positive for Cytokeratin AE1/AE3

Figure 1F: Tumor cells positive for EMA



Immunohistochemistry (IHC) studies usually reveal ES cells with characteristics of both mesenchymal and epithelioid cells. Vimentin, cytokeratins, epithelial membrane antigen, and ETS-transcription factors are all expressed in ES cells [4]. CA125 is also secreted into the bloodstream by ES cells and could be used as a diagnostic and treatment follow up marker [8]. Mixed positive staining for epithelial markers, cytokeratins, vimentin, and CD34, helps differentiate ES from carcinoma. Other immunohistochemical findings are negative staining for nuclear INI1, and S100. It is reported that SMARCB1 (integrase interactor 1) loss is seen in over 90% of ES, both distal and proximal type, due to biallelic deletion of the SMARCB1 gene locus or epigenetic dysregulation [9]. INI1 expression is retained in a few patients (especially in older groups or at the abnormal anatomic site), so the diagnosis of ES should always be made with caution [9]. Differences in the expression of regulatory pathways between proximal and distal types of ES have been discovered by transcriptomic analyses of ES samples. Overexpression of MYC affecting the cell cycle, protein synthesis, and chromatin metabolism was found in PES. Increased class 1 human leukocyte antigens (HLA) expression is predicted by enrichment in Notch/Hedgehog and immune system regulation pathways. These findings may explain some of the differences in response to current therapies and point to potential study and clinical trial directions in the future [12]. We believe that more investigations into the molecular biology and genetics of the ES is needed. Molecular testing were not performed on samples from our patient.

Wide surgical excision is the preferred treatment for ESs with no metastases, though selected patients may undergo adjuvant high-dose chemotherapy or radiotherapy to minimize potential local relapse. [10,11]. When compared to other forms of soft tissue sarcomas, regional lymph node involvement is more common (>20%). When lymph node metastasis is present, therapeutic lymph node dissection is recommended [13]. Lymph nodes metastasis was noted in 3 out of 12 lymph nodes in our patient.

In advanced ES, there is no strong evidence on effectiveness of systematic therapy. The majority of the evidence comes from limited observational studies, case reports, and single patients with ES who were treated in soft tissue sarcoma clinical trials. The most extensive proof comes from a multi-institutional case series by Frezza et al. The study collected data on 115 patients with advanced or metastatic ES who were not given chemotherapy in perioperative settings. In 85 patients, anthracycline-based regimens (anthracycline alone or in combination with ifosfamide or other cytotoxic drugs) were the most common treatment [15]. The Food and Drug Administration (FDA) recently approved Tazemetostat, an EZH2 inhibitor, for the treatment of metastatic or locally advanced ES in adults and children aged 16 and up who are not candidates for radical resection. Tazemetostat has a low toxicity profile, with nausea and fatigue occurring in around 40% of patients [16]. The effectiveness of Tazemetostat is further reinforced by real world report recently published by Dr Sameer Rastogi et al [23]. Recently, limb-sparing surgery has been explored with moderate success [21]. Prior reported cases

of ES location including the uterine cervix [17] and paratesticular region[18]. Martinez et al also reported a case of a PES presented as an incidental adrenal mass [19].

In terms of prognosis, the reported likelihood of ES recurrence varies widely in the literature, ranging from 34% to 87% for recurrence and 30% to 50% for metastasis depending on prognostic factors [4]. Proximal and deep location, rhabdoid characteristics, large size, older age, male sex, necrosis, and vascular invasion are all correlated with a poor prognosis for ES [10,11]. Our patient has some of these negative prognostic factors: proximal location, necrosis, and large size, all of which point to a poor prognosis. The reported 5-year survival rate for epithelioid sarcoma patients is 50-70%, and the 10-year survival rate is 42-55%. Children with epithelioid sarcoma tend to have slightly better outcomes than adults, with 5 year survival rates around 65% [22].

It is clear that epithelioid sarcoma (especially advanced stage, recurrent, or metastasized disease) has been shown to be resistant to traditional cancer therapies, necessitating further exploration of novel treatment methods and techniques. Because of the relatively poor response of epithelioid sarcoma to traditional cancer treatments (surgery, chemotherapy, and radiation), new treatment strategies are being looked to. These include; advanced chemotherapy, Immunotherapies, anti-angiogenic therapies, targeted therapies such as tyrosine kinase inhibitors, selective inhibitors of nuclear export (SINE) compounds, histone deacetylase (HDAC) inhibitors, CDK inhibitors, targeting the cancer stem cell, and oncolytic viral therapy. It is our hope that this report raises awareness of what remains an unmet need in Epithelioid sarcoma management and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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REFERENCES

1. Enzinger FM. Epithelioid sarcoma. A sarcoma simulating a granuloma or a carcinoma. *Cancer*. 1970;26:1029-1041.
2. Armah HB, Parwani AV. Epithelioid sarcoma. *Arch Pathol Lab Med*. 2009;133(5):814-819.
3. Elsamna ST, Amer K, Elkattawy O, Beebe KS. Epithelioid sarcoma: Half a century later. *Acta Oncol*. 2020;59:48-54.
4. Czarnecka AM, Sobczuk P, Kostrzanowski M, Spalek M, Chojnacka M, Szumera-Cieckiewicz A, et al. Epithelioid Sarcoma-From Genetics to Clinical Practice. *Cancers (Basel)*. 2020;12(8):2112.
5. Santos LM, Nogueira L, Matsuo CY, Talhari C, Santos M. Proximal-type epithelioid sarcoma - Case report. *An. Bras. Dermatol*. 2013;88(3):444-447.
6. Siontis BL, Chugh R, Schuetze SM. The Potential of Emerging Therapeutics for Epithelioid Sarcoma. *Expert Opin. Orphan Drugs*. 2017;5:983-989.



7. Hasegawa T, Matsuno Y, Shimoda T, Umeda T, Yokoyama R, Hirohashi S. Proximal-type epithelioid sarcoma: a clinicopathologic study of 20 cases. *Mod Pathol*. 2001;14:655-663.
8. Hoshino M, Kawashima H, Ogose A, Kudo N, Ariizumi T, Hotta T, et al. Serum CA 125 Expression as a Tumor Marker for Diagnosis and Monitoring the Clinical Course of Epithelioid Sarcoma. *J. Cancer Res. Clin. Oncol*. 2010;136:457-464.
9. Hornick JL, Dal Cin P, Fletcher CDM. Loss of INI1 Expression Is Characteristic of Both Conventional and Proximal-Type Epithelioid Sarcoma. *Am. J. Surg. Pathol*. 2009;33: 542-550.
10. Thway K, Jones RL, Noujaim J, Fisher C. Epithelioid Sarcoma: Diagnostic Features and Genetics. *Adv Anat Pathol*. 2016;23(1):41-49.
11. Zhang Y, Liu F, Pan Y, Liang J, Jiang Y, Jin Y. Clinicopathological analysis of myxoid proximal-type epithelioid sarcoma. *J Cutan Pathol*. 2018;45(2):151-155.
12. Frezza AM, Sigalotti L, Del Savio E, Baldazzi D, Sbaraglia M, Righi A, et al. Epithelioid Sarcoma: Molecular Insights into Proximal versus Classic Variant. *J. Clin. Oncol*. 2020; 38:e23552.
13. Keung EZ, Chiang YJ, Voss RK, Cormier JN, Torres KE, Hunt KK, et al. Defining the Incidence and Clinical Significance of Lymph Node Metastasis in Soft Tissue Sarcoma. *Eur. J. Surg. Oncol*. 2018;44:170-177.
14. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in *Ann Oncol*. 2018 Oct 1;29(Suppl 4):iv268-iv269]
15. Frezza AM, Jones RL, Lo Vullo S, Asano N, Lucibello F, Ben-Ami E, et al. Anthracycline, Gemcitabine, and Pazopanib in Epithelioid Sarcoma: A Multi-institutional Case Series. *JAMA Oncol*. 2018;4: e180219.
16. Stacchiotti S, Schoffski P, Jones R, Agulnik M, Villalobos VM, Jahan TM, et al. Safety and Efficacy of Tazemetostat, a First-in-Class EZH2 Inhibitor, in Patients (Pts) with Epithelioid Sarcoma (ES) (NCT02601950). *J. Clin. Oncol*. 2019;37:11003.
17. Suárez-Zamora DA, Barrera-Herrera LE, Rodríguez-Urrego PA, Palau-Lázaro MA. Proximal-Type Epithelioid Sarcoma: Report of an Unusual Case in the Uterine Cervix. *Int J Surg Pathol*. 2017;25(5):468-471.
18. Stephen NS, Gochhait D, Dehuri P, Subramanian H, Goldar RS. Cytomorphology of Proximal Epithelioid Sarcoma in the Paratesticular Location. *Cytopathology*. 2018;29:386- 389.
19. Martinez VP, Nicholson M, Patel T. Abnormal Adrenal Mass Presents as Proximal Epithelioid Sarcoma. *Case Rep Urol*. 2020; 2020:8864218.
20. DeGroot, Henry; Ellison, Bruce. "Limb Salvage Surgery for Extremity Sarcomas". Archived from the original on 2015-02-08. Retrieved 2015-04-23
21. Early clinical and metabolic response to tazemetostat in advanced relapsed INI1 negative epithelioid sarcoma Ghazal Tansir, Sameer Rastogi, Shamim Ahmed Shamim, and Adarsh Barwad Future Science OA <https://www.future-science.com/doi/full/10.2144/fsoa-2020-0173>
22. Casanova, Michela; Ferrari, Andrea; Collini, Paola; Bisogno, Gianni; Alaggio, Rita; Cecchetto, Giovanni; Gronchi, Alessandro; Meazza, Cristina; Garaventa, Alberto; Di Cataldo, Andrea; Carli, Modesto (2006). „Epithelioid sarcoma in children and adolescents“. *Cancer*. 106 (3): 708-17. doi:10.1002/cncr.21630. PMID 16353216. S2CID 25321347