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Para-Vulvar Proximal Epithelioid Sarcoma (ES) with Yolk Sac Differentiation: A Case Report

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Abstract

Background: Epithelioid Sarcoma (ES) of the vulva is a rare and an aggressive malignant soft tissue neoplasm. It is classified into distal, conventional (classic), and proximal types. Presence of morphologic and immunehistochemichal markers of yolk-sac differentiation may represent morphologic variants of SMARCB1-deficient tumors rather than primary vulvar germ cell neoplasia.

Methods: A retrospective reporting of a rare case of para-vulval Epithelioid Sarcoma (ES) proved histologically to be undifferentiated tumor with “yolk sac” elements.

Results: We report a case of 25-year-old lady, medically free; was referred to our hospital following an excisional biopsy of a painless 7X5 cm-sized lump just outside the right labia majora, at a private hospital. Histopathologic examination revealed proximal type ES with infiltrated skin margin. Chest/Abdomen/Pelvis CT with contrast was free. After MDT discussion; wide local excision and bilateral inguinal lymphadenectomy were performed.

The postoperative histopathology revealed free tumor safety margin while right inguinal lymph nodes were invaded with undifferentiated tumor with yolk sac elements. Immunehistochemical study was done and confirmed diagnosis of “INI 1-deficient malignant neoplasm with yolk sac tumor” that was confirmed by strong positive SALL4 and focal positive alpha-fetoprotein. The case was discussed again in the tumor board and advised to start adjuvant chemotherapy. However, the tumor progressed and metastasized to lungs during chemotherapy and unfortunately died after 19 months.

Conclusion: Para-vulval epithelioid sarcoma expressing yolk-sac markers is a rare aggressive tumor. Immunohistochemistry is essential to confirm diagnosis. A multidisciplinary approach of management is the cornerstone of management.

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Introduction

Vulvar malignancy is the fourth most common among female gynecological malignancy, representing 5% of all genital tract malignancy. Histological types of vulvar malignancy include: Squamous cell carcinoma, the most common type, followed by melanoma, sarcoma, and basal cell carcinoma. Primary vulvar sarcomas are rare, reaching an incidence of 1.5 to 5% of cancers in this anatomical region. with leiomyosarcoma as the most frequent type. Epithelioid sarcoma of the vulva is extremely rare and comprises approximately 1% of soft tissue sarcomas [1].

Epithelioid Sarcoma (ES) is a rare and an aggressive malignant soft tissue neoplasm. It is classified into distal, conventional, or classic type and proximal type based on its occurrence in the upper and lower or in the trunk, pubic region, and deeper soft tissues of the external genital tract respectively [2,3]. ES is characterized by tumor cells showing epithelioid morphology and immunohistochemically, characteristic loss of INI1 and its gene coding SMARCB1 in most cases. It was reported to occur in middle-aged women with usual presentation of a solitary painless lump that may be confused with a benign lesion [4]. The prognosis is poor as it is a highly aggressive neoplasm with a high rate of recurrence and metastasis [5].

Given their rarity, the treatment guidelines for ES have been similar to other adult soft tissue sarcomas, with surgical excision in the case of localized disease with safety margins of more than 2 cm [1,5]. Therapeutic lymph node dissection is justified in the presence of lymph node metastasis. Radiation and chemotherapy are used in the advanced, recurrent and metastatic setting; however, their role in the adjuvant setting is uncertain [5]. Anthracycline and gemcitabine-based regimens have shown some benefit in cases of unresectable or metastatic ES. [6].

Furthermore, presence of primary extragonadal yolk sac tumor is very rare. Wang et al [7] reported two cases of Extragonadal Yolk Sac Tumor (EGYST) detected in young females, including one in the myometrium and another in the anterior wall of uterus. Mayhew et al [8] reported a series of vaginal yolk sac tumors who were treated with chemotherapy and conservative surgical management. Moreover, other authors reported that vulvar yolk sac tumors are somatically derived SMARCB1 (INI-1)-deficient neoplasms [9,10].

Case presentation

A 25-year-old parous lady (G3P3A0) was referred to our hospital following an excisional biopsy of a painless 7X5 cm-sized lump just outside the right labia majora, at a private hospital. The patient gave history that the mass appeared 2 months earlier and it started by 2 cm size then progressive increasing size till it reached this size when the patient asked for medical advice. Superficial ultrasound was done, on which the decision of excision was taken, and reported a well-defined capsulated vascular mass suggestive for epidermoid inclusion cyst. Histopathology of the excised lump showed poorly differentiated tumor (with possibility of extra-gonadal germ cell tumor) with infiltration of the margins (Figure 1). The patient was discussed in the weekly local MDT at our hospital and revision of pathology, IHC, and metastatic work up were recommended. The IHC was done and revealed INI 1 deficient vulvar sarcoma in favor of proximal type epithelioid sarcoma (Figure 2). Other IHC markers which were done included: SALL4, glypican-3, CK & EMA, CD34, CD99, Bcl2, CD30, desmin, PLAP, OCT3/4, and GFAP. The metastatic work up revealed free chest, abdomen, and pelvis apart from few enlarged inguinal nodes. The surgery decided for this patient is wide local excision with 2 cm safety margin and bilateral inguino-femoral lymphadenectomy. Frozen section examination confirmed safety margins all-around of the primary tumor. The surgical defect resulted after wide local excision was large enough not to be closed by primary suturing, so plastic V-Y flap was performed to close the defect (Figure 3).

The postoperative histopathology revealed free tumor safety margin while right inguinal lymph nodes were invaded with “INI 1-deficient malignant neoplasm with yolk sac element” that was confirmed by strong positive SALL4 and focal positive alpha-fetoprotein and negative INI 1 immunehistochemistry.

According to our tumor board recommendation and based on postoperative pathology that revealed yolk sac tumor ; the patient was planned to receive adjuvant chemotherapy PEB protocol (bleomycin 30 IU intravenous on days 1, 8, and 15 plus etoposide 100 mg/m2 IV on days 1-5 plus cisplatin 20 mg/m2 IV on days 1-5; every 21days), the patient received one cycle but lost follow up for two months and returned back with local tumor recurrence, new assessment revealed newly developed multiple malignant looking right external and internal iliac LNs, the largest is seen right external iliac measuring 20x21mm. The patient completed 4 cycles of PEB protocol with stationary response regarding malignant-looking right external and internal iliac LNs and labial soft tissue lesion. Then further two courses were added with a regressive response. However, the patient had grade II-III emesis and grade I myelotoxicity.

Due to unexplained insufficient response, new pathologic revision was done and conformed epithelioid sarcoma with yolk sac differentiation. The case was discussed again in MDT and Ifosfamide - doxorubicin protocol was planned (Doxorubicin 20-25 mg/m 2 IV on days 1-3 plus, Ifosfamide 2000-3000 mg/m 2 IV push bolus 3 hours on days 1-3 plus Mesna 225 mg/m 2 IV over 1 hour before Ifosfamide and at 4 and 8 hours after Ifosfamide / 21-28 days) and then to consider definitive radiotherapy.

Unfortunately, the patient lost follow up again and returned back with local tumor progression (mass occupying the whole right labia majora and upper third of the left labia majora), MRI revealed progressive course as regard the size and extension of previously described right labial soft tissue lesion, measuring about 11x 4.5x 9.5cm with newly developed right labial cutaneous and subcutaneous extension with extension left labia majora, clitoris, and perineum (Figure 3).

In addition to a progressive course as regard the number and size of bilateral inguinal, external iliac and internal iliac LNs, the largest 2x5 cm.

The patient received two courses of ifosfamide, doxorubicin with clinical progression, with grade II emesis and myelotoxicity. Then, the patient was referred to consider definitive radiotherapy but she refused to receive radiotherapy.So, rechallenge with PEB with (omission of bleomycin) protocol was tried with stationary response after 2 cycles, MRI revealed near-stationary course as regard previously described right labial soft tissue mass infiltrating perineum, contacting urinary bladder neck and extending in to left labia with cutaneous and subcutaneous infiltration, measures 10,5 x 5 x 8cm with a near stationary course as regard bilateral external iliac & inguinal LNS. CT chest revealed assessment revealed lung metastasis. The patient was planned to receive palliative radiotherapy 40GY and to continue palliative chemotherapy. The

patient didn't continue palliative radiotherapy and developed rapid progression of lung metastasis and unfortunately died because of respiratory failure with overall survival duration of 19 months.

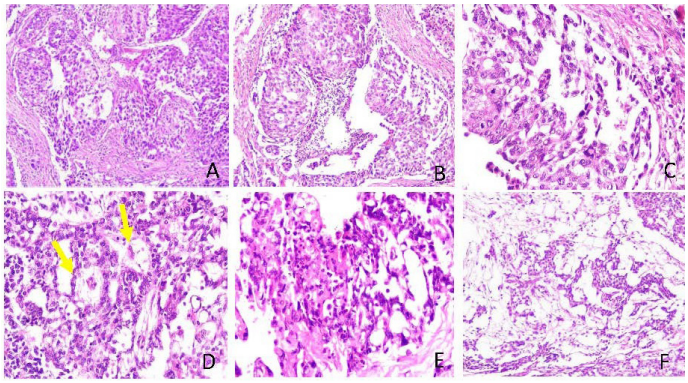

Figure 1: Epithelioid sarcoma, growing in a multinodular pattern, comprised of large epithelioid to polygonal cells arranged in sheets and nests, consistent with typical-appearing epithelioid sarcoma cells exhibit marked cytological atypia, vesicular nuclei and prominent nucleoli (A, B and C).

Foci of the tumor consisted of reticular and microcystic patterns reminiscent of yolk sac tumor -like morphology (D, E and F) with Schiller-Duval bodies formation (D, Arrows) (H&E:200X).

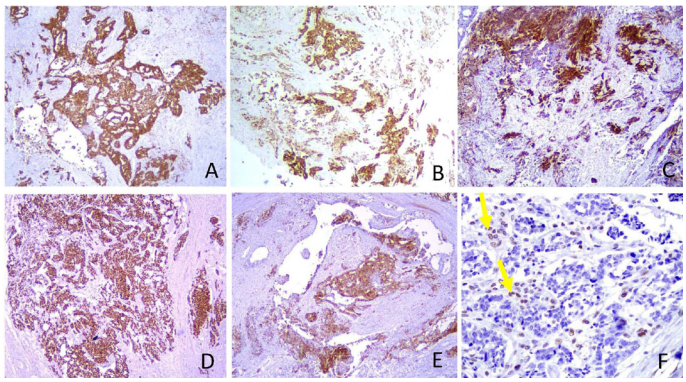

Figure 2: Immunohistochemistry of Epithelioid sarcoma (ES) is diffusely positive for Pan CK **(A)**, EMA **(B)** and CD34**(C)** SALL4 was diffusely positive in the YST-like areas **(D)**, glypican-3 was diffusely positive in the YST-like areas **(E)**. SMARCB1 (INI-1) showed complete loss of expression in both the typical-appearing ES and YST-like components **(F)** while lymphocytes and stromal cells stained positive serving as a positive internal control (Arrows) (DAB 200X).

Discussion

Proximal epithelioid sarcoma of the vulva is very rare tumor, there are only 45 cases described in the English literature. The prognosis of Epithelioid Sarcoma (ES) is not favorable, the lack of symptoms added to its aggressive nature with a rapid tendency to metastasis and high recurrence rate, despite the presence of wide negative margins, cause a not very long survival in these patients. The overall survival rate is 21 months for the initial stages and 6 months for the advanced stages of the disease [2,3]. Locoregional lymph node involvement, vascular invasion, tumor size greater than 2 cm, depth of involvement, presence of necrosis, and high mitotic index, exceeding 2 mitoses per 10 high-power fields, are considered as poor prognostic factors [5,11]

Loco-regional lymph node dissection is controversial, Kim et al. [11] proposed the dissection of enlarged nodes, even though, there is no evidence that it has a significant impact on

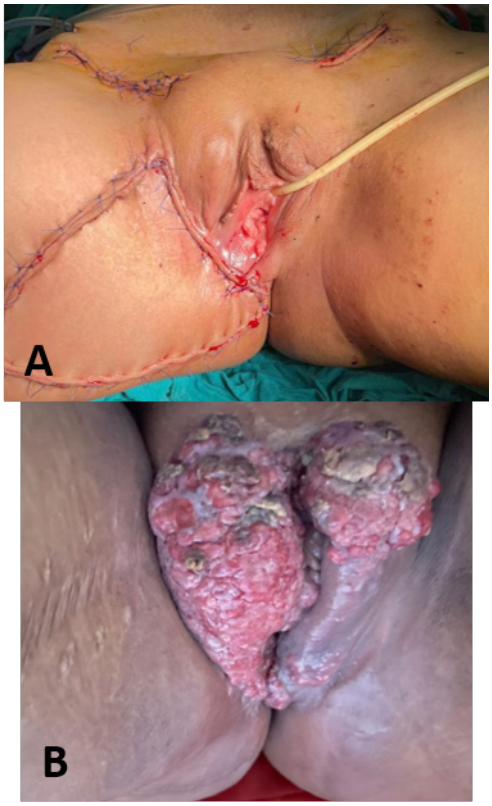

Figure 3: Gross picture. **A:** Postoperative picture, Vulvar reconstruction with V-Y plastic flap after wide local excision with safety margin and bilateral inguino-femoral lymphadenectomy. **B:** The lesion after recurrence and progression and affecting both labia, perineum, clitoris, and mons pubis with necrosis.

local or distant relapse [11] In contrast, Kasumatsu et al. [12] suggested that radical resection and inguinal dissection is the best choice since it offers better control of disease and could postpone adjuvant treatment.

In the reported case, the diagnosis of para-vulvar proximal epithelioid sarcoma expressing germ-cell markers. It was confirmed by pathology revision many times by specialized gynecologic pathologists and IHC that revealed strong positive SALL4 and focal positive alpha-fetoprotein and negative INI-1. These findings suggest that vulvar tumors with pure yolk sac-like morphology may represent morphologic variants of SMARCB1-deficient tumors and not veritable germ cell neoplasia as reported by other authors [9,10].

The response of the case to treatment was poor. Immediately after confirming the diagnosis; the chemotherapy protocol of germ cell tumor was initiated with incomplete response. After rediscussing the case in our MDT; the chemotherapy protocol was changed to Ifosfamide - doxorubicin protocol with unfortunately progression, pulmonary metastasis and mortality. Another factor that worsened prognosis in the reported case is dropped follow up and discontinuation of the scheduled chemotherapy courses twice. The response to treatment and prognosis of vulval epithelioid sarcoma with yolk-sac differentiation is poor that necessitating more studies to identify the best treatment strategy.

Conclusion

Para-vulval epithelioid sarcoma with yolk sac differentiation is a rare aggressive tumor. Immunohistochemistry is essential to confirm diagnosis. A multidisciplinary approach of management is the cornerstone of management.

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Conflicts of interests: No.

Ethical considerations

The report was approved by the Institutional Research Board (IRB), Faculty of Medicine, Mansoura University (Code: R.23.02.2065 - 2023/02/15).

A consent was obtained from the lady to publish her anonymous data.

The authors reported no conflict of interests.

Statistical analysis: Not applicable for one case report.

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