Proximal-type Epithelioid Sarcoma of the Vulva: A Case Report

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ABSTRACT

Epithelioid sarcoma is an uncommon mesenchymal malignancy which represents less than 1% of all sarcomas. Rarer still are reports of this tumor initially presenting in the vulva. We report a case of vulvar proximal-type epithelioid sarcoma.

A 52-year-old had a 5-month history of slowly growing papule on the right labia majora. Excision of the mass revealed a tumor composed of large polygonal cells with abundant eosinophilic cytoplasm. An immunohistochemistry panel revealed cytokeratin AE1/AE3 positivity only. She underwent radical vulvectomy with bilateral groin node dissection. The specimen revealed a cream tan, firm, fairly defined mass at the right vulva. Microscopic examination showed a sheet-like growth pattern of large pleomorphic epithelioid cells with large vesicular nuclei and prominent nucleoli. The tumor showed loss of INI1 nuclear expression and absence of CD34 staining. EMA was positive. The case was signed out as proximal-type epithelioid sarcoma of the right vulva. Two months post-operatively, the patient was given concurrent chemotherapy with 5 cycles of cisplatin 40 mg/m^2 and 6600 centigray vulvar intensity-modulated radiotherapy. She had no evidence of disease for five months until repeat workup showed tumor recurrence in the perineum. She was subsequently given 6 cycles of gemcitabine 900 mg/m^2 and gemcitabine 900 mg/m^2 with docetaxel 100 mg/m^2. Two months after, repeat workup showed persistent progressive disease in the vulva. She was subsequently given 4 cycles of doxorubicin 60 mg/m^2 and is for repeat workup.

The immunohistomorphologic features of this tumor, in addition to its unusual location, present a diagnostic challenge. Clues to the diagnosis include an initial presentation as a soft tissue mass and microscopic features showing the presence of epithelioid to spindle cytomorphology with an infiltrative growth pattern. Immunohistochemistry studies revealing the loss of INI1 nuclear expression and expression of epithelial markers would ultimately establish the diagnosis of this rare clinical entity.

Keywords: epithelioid sarcoma, vulvar neoplasms, female urogenital diseases

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INTRODUCTION

Epithelioid sarcoma is a malignant mesenchymal neoplasm that displays an epithelioid cytomorphology and a predominantly epithelial phenotypic expression.[1] The conventional or classic (distal) form has a predisposition to occur in the extremities and exhibits a pseudogranulomatous growth pattern. On the other hand, the proximal (large cell) variant arises mostly in the truncal region and consists of nests and sheets of large epithelioid cells.[1] The classic subtype is twice more often reported in literature with a male to female ratio of 2:1 and 1.6:1 for the classic and proximal subtypes,

respectively.[1] The proximal-type tends to affect patients between the ages of 20 to 65 years and usually arises in deep soft tissue, particularly the truncal tissues.[1] Clinically, it presents as a rapidly growing superficial mass. There are currently 50 published cases of proximal-type epithelioid sarcoma (PES) worldwide, with only one reported local case. [2-15]. The mean age of the patients with PES of the vulva is 39 ± 15.85 years with most patients undergoing local excision as the initial surgical management. In terms of outcome, majority (60%) of the reported cases had no evidence of disease while 28% died of the disease on follow-up. This paper aims to report a case of a 52-year-old female presenting with a vulvar mass, with an emphasis on the immunohistomorphologic features of this unusual tumor and its management.

CASE PRESENTATION

A 52-year-old gravida 1 para 1 had a 5-month history of enlarging papule on her right labia majora with no associated vaginal bleeding and discharge or bowel and bladder changes. The patient has no known genetic disease. She is a known hypertensive on regular maintenance medications with good control. Her first pregnancy was a spontaneous abortion while her second pregnancy was delivered via spontaneous vaginal delivery with no fetomaternal complications. A transvaginal ultrasound revealed a lobulated, hypoechoic, solid, soft tissue mass measuring 3.5 x 3.5 x 2.7 centimeters located at the right labia, with a normal sized anteverted uterus and a thin and intact endometrium. She underwent excision of the mass and histopathologic findings showed a moderately differentiated adenocarcinoma with clear cell pattern and with a tumor size of 5.0 centimeters in largest dimension. The surgical margins were reported as inadequate. She was advised to undergo chemotherapy or radiotherapy, and subsequently transferred to our institution three months after. Repeat physical examination showed a 9.0 x 8.0 centimeter firm, movable and non-tender mass extending from the mons pubis to the right labia majora without urethral and clitoral involvement. Her chest computerized tomography (CT) scan showed subcentimeter ground glass nodules in the apical and anterior segments of the right upper lobe and the inferior lingular segment of the left upper lobe. It was difficult to assess whether these represented metastatic disease or a primary lung malignancy due to their size. A subsequent abdominopelvic magnetic resonance imaging (MRI) showed a fairly defined, irregular, multilobulated, heterogeneously enhancing mass with small cystic components centered in the right labia majora measuring 9.6 x 3.6 x 3.2 centimeters extending superiorly to the mons pubis and to the left labia with a similar-looking focus measuring roughly 1.6 x 1.8 x 2.1 centimeters (Figure 1).

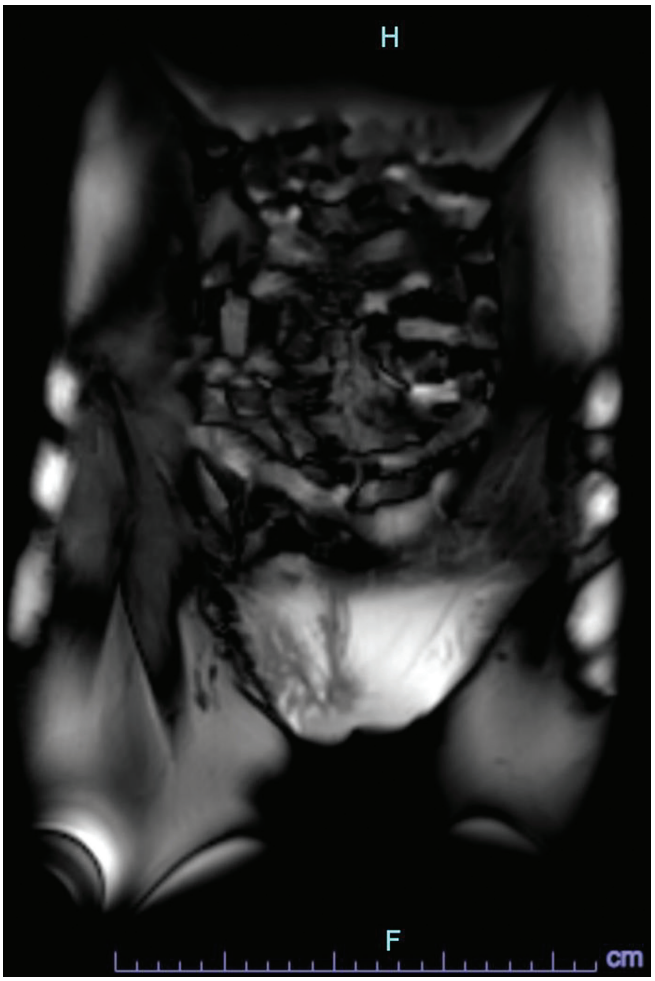

Figure 1. Pelvic MRI of the patient demonstrating the mass centered at the right labia majora.

Her previous biopsy was also submitted for slide review (Figures 2 and 3) which was initially signed out as a round cell neoplasm with epithelioid features. Immunohistochemistry studies, which were readily available in-house, were then performed. The tumor was negative for SMA, inhibin, HMB45, PAX8, CK7, CK20, napsin A, CD10, S100, p40, and periodic acid Schiff with diastase digestion staining. Immunohistochemistry studies with CK AE1/AE3 showed diffuse, strong cytoplasmic staining in neoplastic cells and focal, moderate to strong, nuclear TFE3 expression in some neoplastic cells. Initial differentials at this time include a poorly differentiated squamous cell carcinoma, given the epithelioid morphology of the tumor and its location. This was ruled out due to the p40 negativity. Melanoma is another important consideration given the highly variable morphology of this malignancy but was ruled out by the absence of S100 and HMB45 expression. Other differentials such as clear cell carcinoma, endometrial stromal sarcoma, sex cord stromal tumor, and metastases were also ruled out after the initial panel of stains. The case was initially signed out as favoring a poorly differentiated carcinoma and further studies with INI1 and CD34 were recommended for confirmation but these were deferred until the definitive specimen to avoid further delays in management. She was managed as a case of

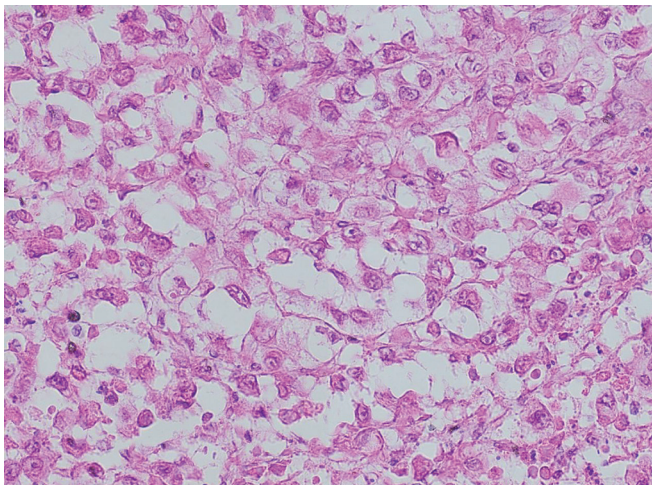

Figure 2. H&E photomicrograph of the initial excision specimen at 400x magnification displaying neoplastic cells with rhabdoid morphology, prominent nucleoli, and some areas exhibiting clear cell changes.

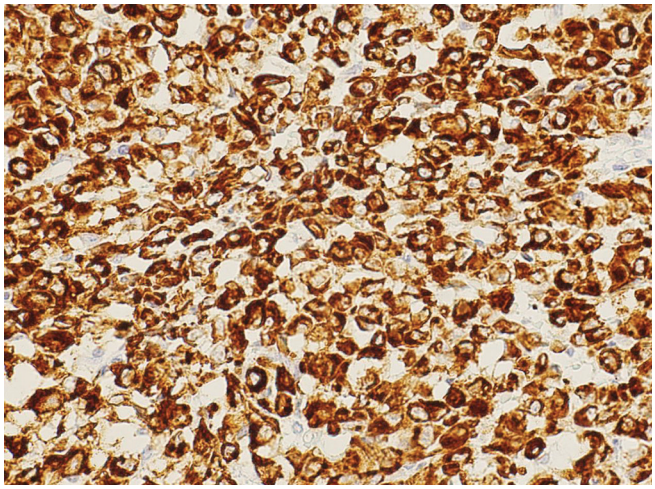

Figure 3. Cytokeratin AE1/AE3 photomicrograph of the initial excision specimen at 400x magnification showing strong diffuse cytoplasmic staining in neoplastic cells.

poorly differentiated malignancy of the vulva, stage IB given the tumor size of more than 2 centimeters and underwent radical vulvectomy with bilateral groin node dissection.

GROSS AND MICROSCOPIC EXAMINATION

Gross examination of the radical vulvectomy specimen revealed a fairly defined, lobulated, cream tan, firm mass located at the right vulva measuring 9.0 x 8.5 x 4.5 centimeters, with focal hemorrhagic areas (Figure 4).

Microscopic examination showed a sheet-like growth pattern of large and pleomorphic epithelioid cells with large vesicular nuclei and prominent nucleoli (Figure 5). Some areas also showed focal stromal myxoid changes.

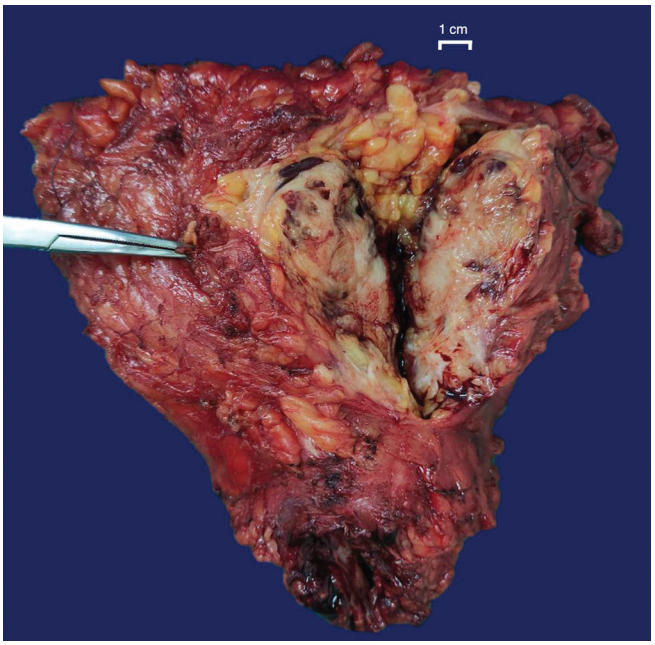

Figure 4. Radical vulvectomy specimen submitted for histopathologic examination showing a fairly-defined, lobulated, cream tan mass with focal areas of hemorrhage.

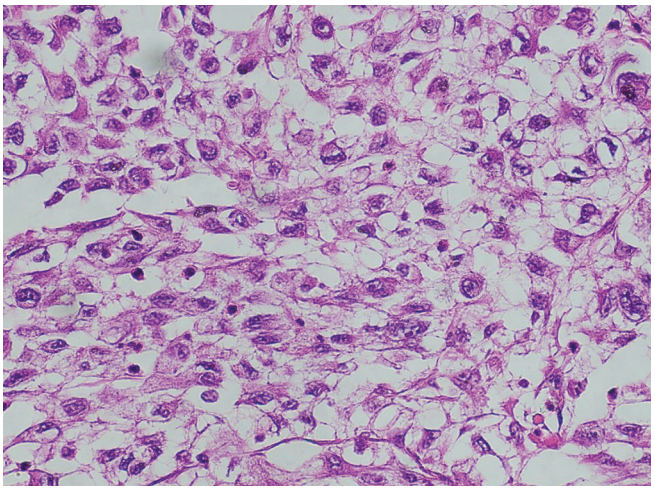

Figure 5. H&E photomicrograph of the radical vulvectomy specimen at 400x magnification showing a similar morphology with the previous biopsy specimen. The cells have a polygonal morphology with moderate to abundant cytoplasm, well-defined cell borders, vesicular nuclei, and prominent nucleoli. Some areas exhibit clear cell changes.

Immunohistochemistry studies for EMA showed patchy cytoplasmic staining (Figure 6). p16 showed patchy nuclear and cytoplasmic staining (Figure 7). CD34 (Figure 8), desmin, and SALL4 were negative. Finally, INI1 showed loss of nuclear expression in neoplastic cells (Figure 9).

The case was eventually signed out as proximal-type epithelioid sarcoma of the right vulva. No definite perineural and lymphovascular space invasion were identified with the nearest margin noted to be less than 0.1 centimeter away. Two out of three superficial inguinal lymph nodes were positive for tumor while the rest of the skin and soft tissue margins as well as one left deep inguinal lymph node were negative for tumor. Her final post-operative diagnosis was epithelioid sarcoma of the vulva, stage IIIB due to the presence of regional lymph node metastases more than 0.5 cm. Two months after her operation, the patient was given concurrent chemotherapy with 5 cycles of cisplatin 40 mg/m^2 and 6600 centigray vulvar intensity-modulated radiotherapy. She had no evidence of disease for five months until repeat workup showed tumor recurrence in the perineum. She was subsequently given 6 cycles of gemcitabine 900 mg/m^2 and gemcitabine 900 mg/m^2 with docetaxel 100 mg/m^2. Despite chemotherapy, repeat workup showed persistent progressive disease in the vulva after two months. She was subsequently given 4 cycles of doxorubicin 60 mg/m^2. The patient was able to adhere to the radiotherapy and chemotherapy regimen, with good tolerability. During the course of her treatment, there was wound dehiscence over the vulvar graft site. Currently, there is wound persistence in the area, which is being managed by normal saline wound dressing. The patient is still for repeat workup at the time of writing.

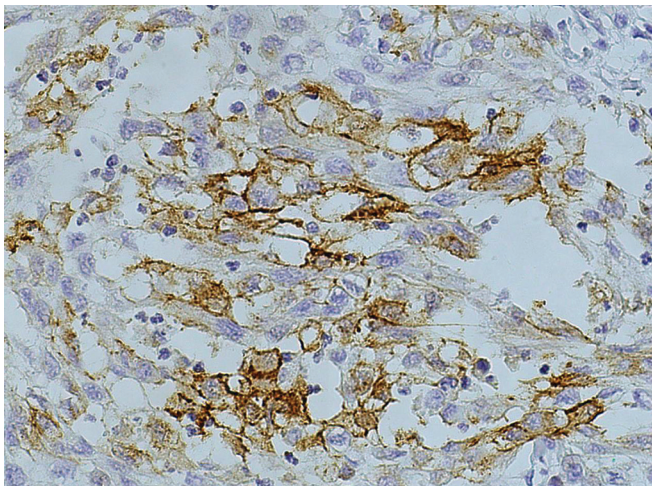

Figure 6. EMA photomicrograph of the radical vulvectomy specimen at 400x magnification showing patchy cytoplasmic staining.

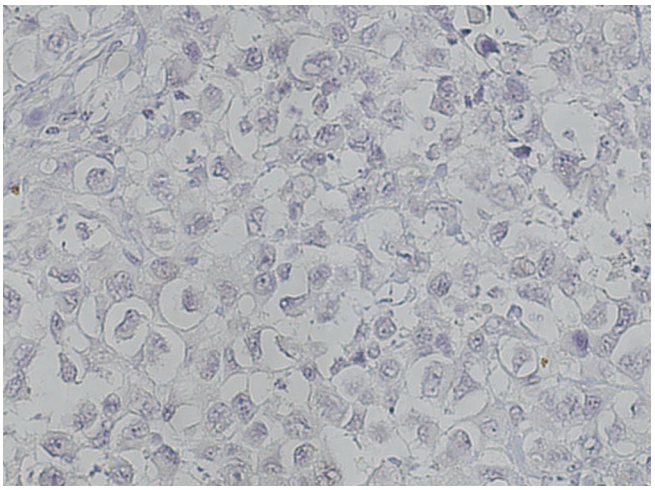

Figure 8. CD34 photomicrograph of the radical vulvectomy specimen at 400x showing no staining.

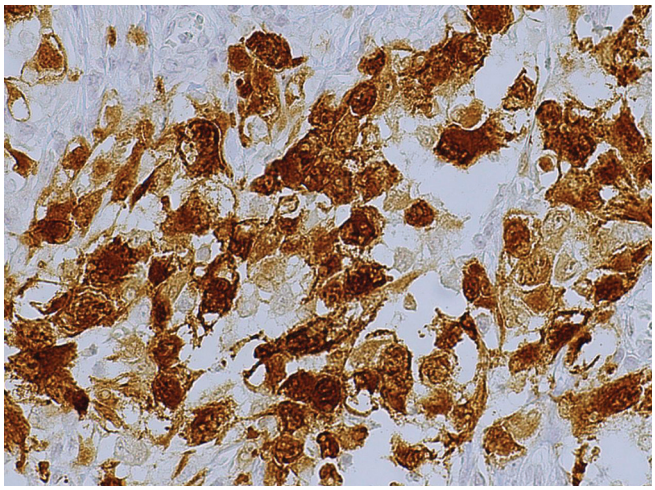

Figure 7. p16 photomicrograph of the radical vulvectomy specimen at 400x showing patchy nuclear and cytoplasmic staining.

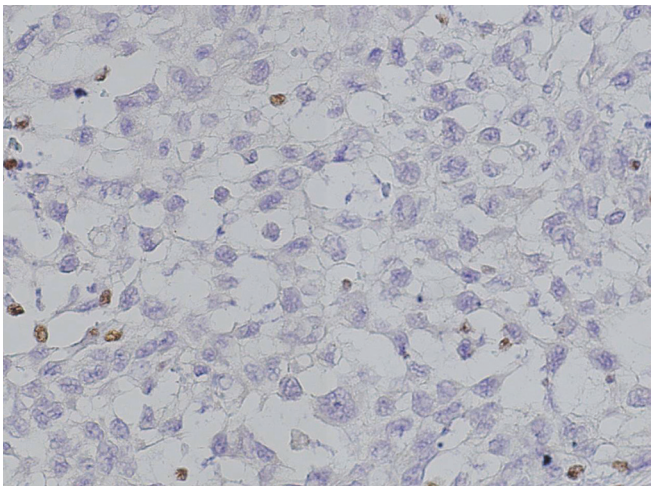

Figure 9. INI1 photomicrograph of the radical vulvectomy specimen at 400x showing loss of nuclear expression in neoplastic cells.

DISCUSSION

Epithelioid sarcoma is a malignant mesenchymal neoplasm that demonstrates partial or complete epithelioid cytomorphology and immunophenotype.[1] The classic (distal) subtype is more common in the extremities, predominantly on the hand and fingers, and has a pseudogranulomatous growth pattern. The proximal (large cell) subtype (PES) is less common and arises mostly in the deep soft tissue of the truncal region. Clinically, it has a larger size, more infiltrative and microscopically consists of nests and sheets of large epithelioid cells. This sarcoma is also able to metastasize to the lymph nodes, as seen in this patient.

Epithelioid sarcoma represents less than 1% of all adult soft tissue sarcomas with PES being less often reported in literature. It has a slight male predominance and usually affects young to middle-aged adults.

Epithelioid sarcoma is associated with almost a complete loss of SMARCB1 (INI1) nuclear protein expression.[1] The SMARCB1 gene, also called BAF47, INI1, or SNF5, located on 22q11.23 is part of the SWI/SNF chromatin-remodelling complex which codes for a protein expressed in normal, non-neoplastic cells.[1] This complex has ATPase activity and serves to change the position of nucleosomes which modulates transcription of genes involved in stem cell biology and differentiation.[1] By immunohistochemistry, recurrent loss of INI1 is seen in a limited variety of tumor types.

The macroscopic appearance of PES usually presents as solitary or multiple whitish nodules. Cut sections may reveal a glistening, greyish white to greyish tan color with pinpoint yellow and brown foci which represents areas of hemorrhage and necrosis. In this patient, the mass was fairly defined and lobulated with cream tan, firm cut sections. Microscopically, PES shows large, sometimes pleomorphic epithelioid (carcinoma-like) cells having large vesicular nuclei and prominent nucleoli with a multinodular and sheet-like growth pattern.[1] Cells with rhabdoid features are more common in the proximal-type wherein differentiation from extrarenal rhabdoid tumor becomes challenging when the rhabdoid cell is the predominant cell type. Some cases may have a myxoid stroma, as seen in this case.

Both classic and PES show immunoreactivity for epithelial markers including low- and high-molecular-weight cytokeratins and EMA. Majority of the cases express CK8 and CK19 but are typically or only focally positive for CK5/6. Unlike carcinomas, more than 50% of epithelioid sarcomas express CD34 which is not exhibited in this case. Loss of INI1 expression occurs in most cases for both types.

Diagnosing epithelioid sarcoma based on morphology alone can be difficult since other entities may show histomorphologic features of having neoplastic cells with similar epithelioid morphology. Differentials include poorly differentiated carcinoma, rhabdoid tumor, other sarcomas with epithelioid morphology, and melanoma. Establishing the diagnosis of epithelioid sarcoma would rest on the proper clinical context such as age, sex predominance, location, and imaging findings. Considering this clinical information would guide and direct subsequent immunohistochemistry studies. Ultimately, the essential features required for the diagnosis of epithelioid sarcoma would be the presence of diffuse or nodular pattern of growth of epithelioid cells with abundant eosinophilic cytoplasm, some degree of EMA or keratin positivity, and loss of INI1 (SMARCB1) expression. Focal CD34 expression is desirable but this is not present in all cases.[1] Our case showed reactivity for epithelial markers CK and EMA, no reactivity for CD34, and loss of INI1 expression.

The 5-year and 10-year overall survival rates of epithelioid sarcoma are 45-70% and 45-66%, respectively.[1] However, more specific data regarding the overall survival rates and prognosis in PES of the vulva is limited. Among the 50 published cases of PES of the vulva reviewed for this case report, majority (60%) had no evidence of disease (mean follow-up time = 40 months, SD = 39 months) while 28% died of the disease (mean follow-up time = 17 months, SD = 20 months). For epithelioid sarcoma in general, a deeper location correlates with lower overall survival which accounts for the poorer survival associated with PES. The rates of local recurrence, lymph node dissemination, and metastasis for localized epithelioid sarcoma are 14-25%, 34-52%, and 33%, respectively.[1] Other adverse prognostic factors include older age, higher grade or mitotic activity, nodal involvement, tumor size more than 5 centimeters, and proximal-type histology with the presence of rhabdoid cells. In this patient, the following adverse prognostic factors are present: nodal involvement, tumor size more than 5 centimeters, and proximal-type histology. Multimodal management for epithelioid sarcoma is said to be associated with better control rates when surgery is combined with chemotherapy or neoadjuvant radiotherapy.[1] More specific data regarding the utility of adjuvant therapy such as chemotherapy or radiotherapy for PES of the vulva are still not yet established due to the limited number of cases.[2] Wide surgical resection remains to be the primary treatment modality for localized epithelioid sarcoma and neo-adjuvant or adjuvant therapy may be recommended as it is associated with a lower rate of recurrence.[13] The patient underwent radical vulvectomy with bilateral groin node dissection since the initial excision had positive margins, the tumor was bulky, and the mass occupied the mons pubis above the inguinal canal with the mass crossing the midline. The goal was to obtain adequate surgical margins of at least 1 centimeter. Given the close surgical margins of resection, adjuvant radiotherapy was advised to improve outcomes. Cisplatin was given weekly as a radiosensitizer while she was receiving vulvar intensity-modulated radiotherapy. There was tumor recurrence after five months, hence, she was given 6 cycles of gemcitabine and docetaxel which is the standard chemotherapy regimen for advanced, recurrent or persistent soft tissue sarcomas. Finally, 4 cycles of doxorubicin were given as second-line

chemotherapy due to her persistent progressive disease. The patient is still for repeat workup at the time of writing. If there is partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines after the 4th cycle, doxorubicin can still be continued until 6 cycles. However, if there is disease progression, molecular profiling tests can be performed so that more specific targeted treatment can be given.

CONCLUSION

In conclusion, we have presented a case of PES of the vulva, highlighting its histopathologic features, the challenges associated with its diagnosis and the management given for our case. PES is an uncommon malignant mesenchymal neoplasm which represents less than 1% of all sarcomas. This tumor shows an epithelioid cytomorphology which can be difficult to differentiate from other neoplasms exhibiting the same morphology. Arriving at the diagnosis would rest on a compatible clinical picture such as an initial presentation as a soft tissue mass and the presence of epithelioid to spindle cytomorphology with infiltrative growth pattern. Immunohistochemistry studies revealing the loss of INI1 nuclear expression, and presence of staining for EMA and cytokeratin would ultimately establish the diagnosis of this rare clinical entity.

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Ethical Statement

Written informed consent was obtained from the patient.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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