

Case report

Epithelioid angiosarcoma of the vulva: A case report

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1. Introduction

Angiosarcoma is a rare malignancy of lymphatic or vascular endothelium that can arise anywhere in the body (Young et al., 2010). Angiosarcomas make up approximately 2% of soft tissue and 5.4% of cutaneous sarcomas. Chronic lymphedema and radiation treatment are each known risk factors for development of angiosarcoma, which has been well described primarily in patients treated for breast cancer (Huang and Mackillop, 2001). Lymphangiosarcoma occurring secondary to chronic lymphedema in patients who had undergone mastectomy was first reported in 1948 and is now known as Stewart-Treves syndrome (Stewart and Treves, 1948). Angiosarcomas of gynecologic origin are rare, with only 4 reported in the literature. We present a case of vulvar epithelioid angiosarcoma associated with radiation and chronic lymphedema.

2. Case report

The patient initially presented at age 85 with abdominal pain, vomiting, and vaginal bleeding. Dilatation and curettage was performed, revealing a grade 2 endometrioid adenocarcinoma of the uterus. She had an excellent performance status and desired aggressive surgical treatment. Minimally invasive hysterectomy with bilateral salpingo-oophorectomy and removal of pelvic and para-aortic lymph nodes was performed and final pathology was consistent with FIGO stage II papillary serous adenocarcinoma of the uterus. Postoperative imaging showed no other evidence of disease. Multimodality therapy was recommended, and she received a total of 6 cycles of carboplatin with paclitaxel and whole pelvic radiation therapy in sandwich fashion. A total of 45Gy in 1.8Gy daily fractions of whole pelvic radiation was given over 35 days. Within 6 months, she developed unilateral lymphedema in her right lower extremity, which did not resolve despite treatment with lymphedema therapy (Fig. 1A). By the staging guidelines of the International Society of Lymphology she would be characterized as having Stage III lymphedema (International Society of Lymphology, 2013). She followed up for 5 years with continued stable lymphedema, but no evidence of recurrent disease.

Approximately 6 months after her last follow up visit, at the age of

90, she presented with an asymptomatic vulvar rash. It was unclear how long the rash had been present, as the patient developed dementia and did not notify her caretaker until immediately prior to the visit. She denied trauma to the area, pain, bleeding or fever. Examination revealed a 20 × 10 cm area of purple and red hyperpigmentation of the labia majora extending to the mons pubis with unchanged longstanding induration, without warmth or drainage (Fig. 1B). Examination of the vagina and pelvis was normal. A punch biopsy was performed and the patient was treated with antibiotics for possible cellulitis. CT scan of the pelvis showed thickening of the lower abdominal and pelvic wall without discrete mass. Pathologic evaluation revealed grade 2 epithelioid angiosarcoma. Histologic sections show an infiltrative lesion dissecting through dermal collagen and abutting the overlying epidermis (Fig. 2A). Tumor cells are epithelioid and vascular channels are present with areas of discohesion. Individual cells have pleomorphic nuclei, prominent nucleoli and basophilic cytoplasm (Fig. 2B). Scattered mitotic figures are identified. Neoplastic cells are positive for vimentin, ERG and CD31 and negative for CD34, CAM5.2, CK7, p63, MART1, S100, ER, PAX8 and CD45 (Fig. 3). The patient's dementia rendered her unable to make decisions and the patient's daughter and power of attorney (POA) declined treatment, electing for hospice enrollment and observation alone. Although her lesion is large and carries a significant risk of metastasis, further imaging was not pursued as the results would not alter the treatment plan. She continued to be asymptomatic with no pain and no drainage or bleeding.

3. Discussion

Vulvar angiosarcomas are rare, this patient having the fifth reported case in the English language literature. Most reported cases of gynecologic angiosarcomas have occurred in the uterus and ovaries. A 2014 review identified 52 angiosarcomas of primary gynecologic origin (Kruse et al., 2014). Of these cases, 29 were ovarian, 18 uterine, 3 vaginal, and 2 vulvar. There are two additional single case reports of vulvar angiosarcoma, one on the mons pubis following chemoradiation for vulvar cancer (Guirguis et al., 2007), the other reported in a patient with no prior radiation therapy or lymphedema (Sheinis et al., 2016). More common locations (in descending order) for angiosarcomas are

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Fig. 1. A) Lymphedema of right leg. B) Gross view of epithelioid angiosarcoma.

the head and neck, breast, extremities, trunk, liver, heart, bone, and spleen (Young et al., 2010).

Clinical diagnosis may be delayed due to its asymptomatic nature and difficulty differentiating between malignancy, trauma or infection. Cutaneous angiosarcomas in general typically present as a violaceous

papule/plaque or a bruise-like appearance as seen in our patient, while deeper lesions typically present as an expanding painless mass (Young et al., 2010). This non-specific presentation can lead to delays in diagnosis, particularly when the patient is not experiencing any discomfort from the lesion.

Pathologic diagnosis of angiosarcoma often requires thorough staining, particularly in poorly differentiated tumors. Histologically, angiosarcomas can have a wide range of appearance, from well-differentiated with endothelial atypia to high grade spindle cell morphology (Hart and Mandavilli, 2011). The epithelioid subtype seen in our patient is so named because unlike other angiosarcomas the morphology resembles epithelial tissue, and thus can be easily mistaken for a carcinoma. Immunohistochemical staining can help differentiate epithelioid angiosarcoma from carcinoma as well as other epithelioid neoplasms. Angiosarcomas of all types are generally positive for vimentin. Epithelioid angiosarcomas are generally positive for factor VIII, CD31, and Fli-1; they are variably positive for CD34, epithelial membrane antigen, and CK (cytokeratin); and negative for S100 (Hart and Mandavilli, 2011). In contrast, a carcinoma would be positive for CK and EMA, but negative for factor VIII, CD31, CD34, and Fli-1. Other epithelioid neoplasms that can be differentiated by immunohistochemical staining include malignant peripheral nerve sheath tumor, epithelioid sarcoma, melanoma, malignant mesothelioma, anaplastic large cell lymphoma, and epithelioid hemangioendothelioma.

The etiology of vulvar angiosarcoma, like other angiosarcomas, may lie in longstanding lymphedema and radiation therapy. An analysis of SEER (Surveillance, Epidemiology, and End Results) data found a standardized incidence ratio of 26.2 for development of angiosarcoma in breast cancer patients who had undergone radiation therapy compared to the general female population (Huang and Mackillop, 2001). The maximum elevated risk occurred 5–10 years following diagnosis of breast carcinoma. The link between chronic lymphedema and angiosarcoma has been established with over 400 cases of Stewart-Treves syndrome reported in the literature, as well as case reports of angiosarcoma associated with lymphedema of other causes such as filariasis and trauma (Sharma and Schwartz, 2012). Risk factors other than radiation and chronic lymphedema that have been identified include certain toxic exposures (vinyl chloride, thorium dioxide, arsenic, anabolic steroids), foreign bodies, and some familial syndromes (including BRCA mutations) (Young et al., 2010).

The literature supports surgical excision as the primary treatment of choice for angiosarcoma, although the prognosis remains poor even with early intervention (Sharma and Schwartz, 2012). Locoregional and systemic chemotherapy have shown little success in improving survival (Young et al., 2010). There are no large studies to guide choice of therapy, but the most commonly used drugs include the anthracyclines, taxanes, and ifosfamide. Radiation therapy is often employed as adjuvant treatment but there is no compelling data recommending its use, and at least one study has shown no benefit compared to adjuvant chemotherapy. Among the vulvar angiosarcoma cases in the literature, treatment approaches have included surgical excision in all cases with adjuvant radiotherapy and/or chemotherapy in most (Kruse et al.,

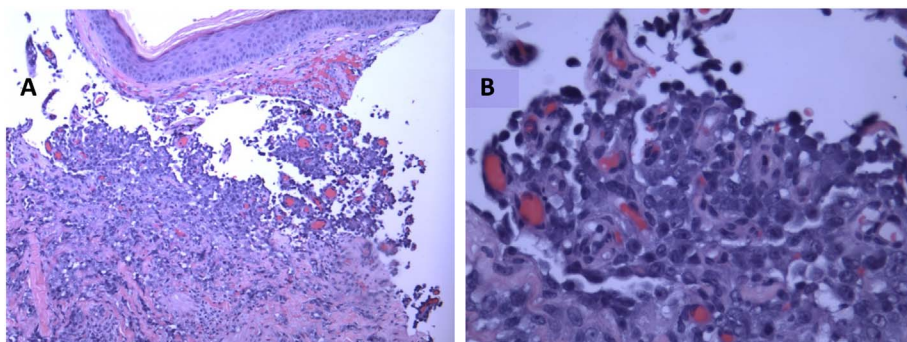


Fig. 2. H & E staining: A) 200 × magnification demonstrating dissection through dermal collagen, epithelioid morphology, vascular channels. B) 400 × magnification demonstrating pleomorphic and prominent nucleoli, basophilic cytoplasm, and scattered mitotic figures.

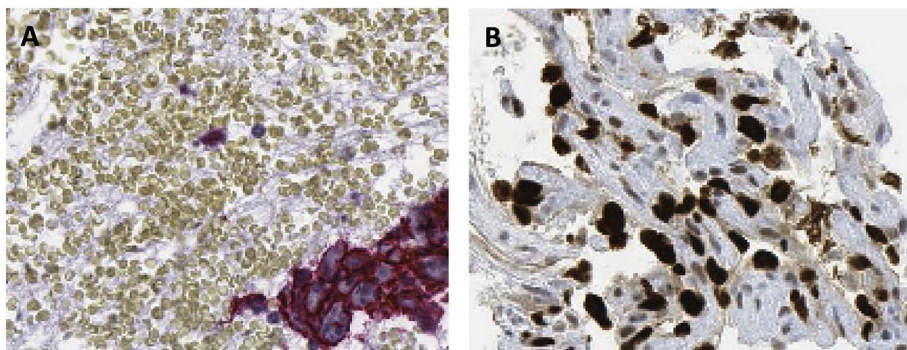


Fig. 3. Immunohistochemical staining at 10 ×: A) CD31. B) ERG.

2014; Guirguis et al., 2007; Sheinis et al., 2016).

Due to the rarity of angiosarcoma, information on prognosis is limited. Epithelioid angiosarcomas tend to metastasize early both to solid organs (especially lungs, bone, soft tissue, skin) and lymph nodes (Hart and Mandavilli, 2011). The overall survival rate for angiosarcomas at 5 years is approximately 35% (Young et al., 2010). The epithelioid subtype is rare enough that no data is available to compare survival to other subtypes. High proliferative index (MIB-1 at least 10%), older age, and larger tumor size are poor prognostic factors (Hart and Mandavilli, 2011). MRI or CT (for visceral and retroperitoneal tumors) can be used to characterize the primary tumor (Ryan and Meyer, n.d.). Chest CT or CXR is indicated for all soft tissue sarcomas, and imaging of the brain is indicated for angiosarcomas.

The case we present helps to illustrate the importance of maintaining a high index of suspicion for the development of angiosarcoma in patients receiving pelvic radiation therapy or who have longstanding lymphedema. Although very few vulvar angiosarcomas have been reported, most of them have occurred following pelvic radiation therapy. Further complicating the diagnosis is the varied clinical presentation; while our patient presented with violaceous skin, the other cases of vulvar angiosarcoma described have presented as painless masses or white papules. Thus, for any suspicious lesion of the vulva, a biopsy should be considered, particularly if it occurs in a previously radiated field or an area of chronic lymphedema. Given the long duration generally seen between radiation and development of angiosarcoma, educating the patient on the importance of returning to the physician if any new lesions develop would be appropriate given that many patients will be outside the window of regular follow up.

Conflicts of interest

The authors certify that they have NO affiliations with or

involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, or beliefs) in the subject matter or materials discussed in this manuscript. Consent to publish was obtained from the daughter and POA of the patient described in this case report.

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