

Rapidly progressive and fatal case of extragenital cutaneous epithelioid angiosarcoma with visceral involvement



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INTRODUCTION

Cutaneous angiosarcomas (CASs) are aggressive malignancies with a poor prognosis. Although rare, most cases are seen 1) on the head and neck of elderly men, 2) in irradiated skin after therapy for breast carcinoma, and 3) in the setting of long-standing lymphedema (Stewart-Treves syndrome). Only 5 cases of cutaneous external genital CAS have been reported, usually in the setting of pelvic radiation for gynecologic malignancies.¹ Here, we describe a case of rapidly progressive and fatal inguinal epithelioid CAS with visceral involvement.

CASE REPORT

A 78-year-old woman presented with a 2-week history of progressive fatigue, abdominal pain, and shortness of breath requiring intensive care. On the mons pubis, she had an ulcerated, 6-cm, purple hemorrhagic exophytic tumor with 2 to 3 cm surrounding ecchymosis and satellite nodules (Fig 1). This lesion was reported to have appeared 4 weeks prior as a purple bump the size of a pencil eraser. As the lesion grew, it sporadically bled. Her history was notable for stage IIIC endometrioid adenocarcinoma with mucinous features that was treated with radical hysterectomy with pelvic lymph node dissection and adjuvant radiation 12 years before presentation, which resulted in chronic bilateral lymphedema of the lower extremities.

One week before hospital admission, a biopsy of the tumor showed a dermal-based proliferation of markedly atypical epithelioid cells with vesicular

Abbreviations used:

CAS: Cutaneous angiosarcoma

nuclei forming ill-defined vascular channels that were immunoreactive for CD31 and ERG. The cells did not stain for AE1/AE3, S100, or HHV8 immunostains (Fig 2).

Computed tomography of the chest and abdomen showed a pneumothorax on the right side with pleural effusion, parenchymal consolidations, and peritoneal nodules on the anterior abdomen suspicious for peritoneal metastases. The patient developed high-volume hemorrhagic pleural effusion with output of 3 to 4 L/d, requiring chest tube placement. The etiology of this pleural effusion was believed to be malignant, although cytology results were negative. Oncology and cardiothoracic surgery specialists were consulted, but chemotherapy and surgical interventions were not considered because of poor functional status. The patient elected comfort care measures and died 5 days after histopathologic diagnosis.

DISCUSSION

Angiosarcomas are aggressive soft-tissue sarcomas derived from malignant endothelial cells, accounting for 1.6% of cutaneous soft-tissue sarcomas.² The most common locations of CAS are the head and neck (27%), breast (20%), and extremities (15%), with primary visceral origin being

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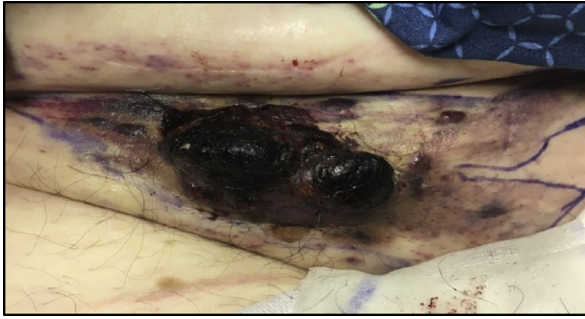


Fig 1. Right mons pubis with 6-cm purple, ulcerative, hemorrhagic, exophytic tumor and a 2- to 3-cm periphery of ecchymosis and satellite nodular lesions.

exceedingly rare.³ Postradiation therapy CAS is the most common subtype, whereas Stewart-Treves syndrome makes up approximately 5% of cases.⁴ Recently, a large population-based study using The Netherlands Cancer Registry found that 0.1% of patients who received radiotherapy developed CAS, with older age and partial mastectomy being risk factors. The median latency for developing CAS was 8 years (range, 3-20 years).⁵ Radiation therapy for other cancers has also been associated with CAS.^{1,3} Only 5 cases of vulvar (or external genital) involvement in CAS have been reported, most of which were associated with prior radiation therapy for a gynecologic malignancy.¹

CAS typically appears as ill-defined ecchymotic patches or purplish, multifocal papules, a nonspecific presentation that can lead to a delay in diagnosis. Untreated, lesions become nodular and ulcerative, reaching sizes larger than 20 cm in advanced cases.³ Histologically, CASs have irregular, anastomosing, and dilated vascular structures with largely inconspicuous endothelial cells that may show pleomorphism and hyperchromatic nuclei. These malignant endothelial cells attempt to recapitulate an infiltrative immature vascular network that dissects collagen bundles and leads to extensive extravasation of red blood cells with hemosiderin deposition.

Histologic variants within CAS include epithelioid, clear cell, foam cell, signet cell, and granular cell.⁴ *Epithelioid*, defined as malignant cells with polygonal or rounded shape with abundant eosinophilic cytoplasm, large vesicular nuclei, and prominent eosinophilic nucleoli, is the best-described variant and is more commonly seen with sporadic (ie, not associated with radiation or lymphedema) CAS.⁶ Epithelioid CASs more commonly show infiltrative sheets of malignant cells in the dermis/subcutis with hemorrhage and, occasionally, necrosis

(40%).⁶ Immunohistochemistry shows expression of endothelial markers such as von Willebrand factor, CD34, CD31, vascular endothelial growth factor, and ERG. ERG, a nuclear stain, is commonly regarded as highly sensitive for angiosarcoma.⁴ The histopathologic differential for epithelioid CAS includes poorly differentiated cutaneous and metastatic carcinomas, melanoma, epithelioid sarcoma, and Kaposi sarcoma. Diagnosis relies on overall morphology and immunohistochemistry, with epithelioid CAS typically showing some degree of vasof ormation and strong CD31 or ERG positivity.⁶

The American Joint Committee on Cancer and the National Comprehensive Cancer Network lack specific grading/staging systems or treatment algorithms for CAS, which fall under the umbrella designation of *soft-tissue sarcoma*. CASs carry a poor prognosis, with a 5-year survival of 45% to 60% and overall survival of 35%.^{2,3,5} No differences in survival exist between sporadic and radiation-associated CAS.⁴ Histologically, the presence of necrosis and epithelioid morphology have been associated with a worse prognosis.⁶ Although most patients present with localized disease, up to 20% have metastatic disease at presentation.⁷ CASs spread hematogenously. The most common site for metastases is the lungs, followed by bone, liver, and regional lymph nodes.⁷

Data on treatment modalities for CAS are limited to retrospective studies and case series. Surgical excision with wide margins, often difficult to achieve because of the ill-defined nature of these neoplasms, is the treatment of choice for resectable CAS. Adjuvant therapy with radiation (considered in non-radiation-induced cases) or chemotherapy (paclitaxel and doxorubicin) has shown mixed results in studies, providing only a marginal survival response. The only prospective phase 2 study of paclitaxel showed a partial response in 18.5% of patients (n = 5) with a progression-free survival of 4 months.⁸

The success of beta blockers in shrinking infantile hemangiomas has led researchers to follow similar logic in other vascular tumors, including angiosarcomas. In 2013, Stiles et al⁹ showed that β -adrenergic receptor blockage with propranolol selectively inhibited proliferation, survival, and migration of malignant cells both in vitro and in vivo. Chow et al¹⁰ reported that propranolol monotherapy at 1 to 1.5 mg/kg reduced the proliferative index in a patient's scalp angiosarcoma by 34% after 1 week of treatment. Receiving a combination of propranolol, paclitaxel, and radiotherapy, the patient had a significant partial response and prolonged progression-free survival.

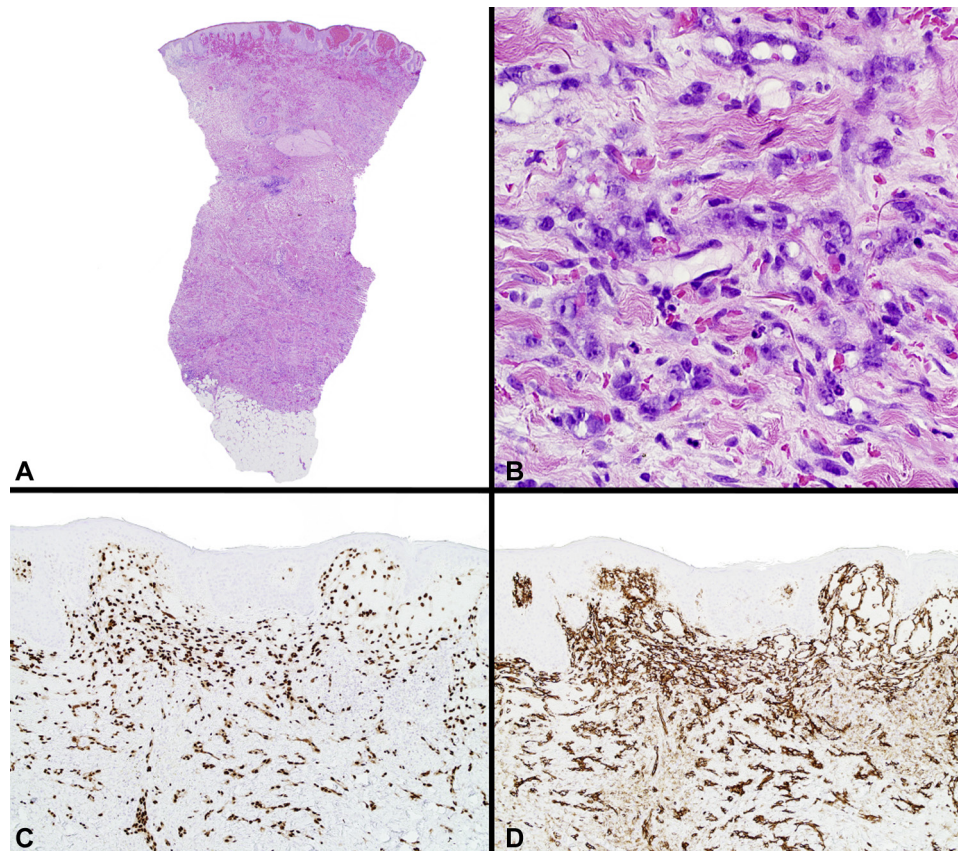


Fig 2. **A**, Punch biopsy sample with a dermal-based proliferation of markedly atypical spindled and epithelioid cells with vesicular nuclei. Original magnification, $\times 20$. The cells form focal anastomosing vascular spaces, but well-formed vascular spaces are largely indistinct. **B**, There was moderate nuclear pleomorphism, hyperchromasia, and atypia seen in the atypical cellular infiltrate. Original magnification, $\times 400$. Scattered mitoses ($3/\text{mm}^2$), hemorrhage, and deposits of hemosiderin were present. Necrosis was absent in the sampled specimen. **C** and **D**, ERG and CD31 immunostains highlight the atypical cells and confirm the vascular histogenesis of the tumor. Original magnifications, $\times 100$. Tumor cells did not stain with HHV-8, S100, or cytokeratin AE1/AE3.

Subsequent case reports have shown similar promising results.

Our case emphasizes the rapid and fatal nature of an extragenital epithelioid CAS with visceral involvement that developed in the setting of prior radiation therapy and chronic lymphedema. Both dermatologists and dermatopathologists should be aware of the uncommon presentations of CAS because a delay in diagnosis could be fatal. When appropriate, beta blockers should be considered an adjunct treatment for CAS.

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