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Case report

# Post-radiation angiosarcoma of the uterine cervix

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## 1. Background

Angiosarcoma is a rare malignant mesenchymal neoplasm of endothelial origin, which comprises 1–2% of all soft tissue sarcomas (Young et al., 2010; Shah et al., 2018). It is a clinically aggressive entity, with a 5-year overall survival of 35% and a mean survival of approximately 7 months (Young et al., 2010; Kruse et al., 2014). Although cutaneous presentations of angiosarcoma are most common, these lesions can arise in essentially any anatomic location, including superficial or deep soft tissue and visceral sites (Weiss et al., 2008). Etiologic factors such as exposure to radiation or chemicals, chronic lymphedema, foreign bodies, and familial syndromes have been established in many cases, although the majority of cases remain idiopathic with no known inciting exposures or predispositions (Young et al., 2010). Only two previous reports of patients with angiosarcoma arising in the uterine cervix exist in the literature - neither of which had previous radiation therapy or other documented known risk factors. The first case report was that of a 65-year-old black woman in Nigeria (Ohayi et al., 2013), and the other was in a 43-year-old woman in the United Kingdom (Shah et al., 2018). To our knowledge, there have been only 6 reported cases of post-radiation angiosarcoma of the female genital/gynecologic tract (Morgan et al., 1989; Tohya et al., 1991; Chan and SenGupta, 1991; Morrel et al., 1993; Virtanen et al., 2007), occurring within the uterine corpus and the vagina, but none in the cervix. The current case highlights an extremely rare case of post-radiation cervical angiosarcoma arising in a patient with a history of radiotherapy for squamous cell carcinoma of the cervix eleven years prior.

## 2. Case summary

A 54-year-old Hispanic woman initially presented to the emergency department (ED) with right lower quadrant abdominal pain and vaginal discharge. Her past medical history was notable for cervical squamous cell carcinoma, status post primary radiation treatment and chemotherapy in 2007 at an outside hospital. Her surgical history included prior cholecystectomy and appendectomy. The patient had been followed regularly by her oncologist without evidence of recurrence and was last seen approximately 6 months prior to presentation at our institution. At that time, she reported faint vaginal spotting and underwent cervical biopsies which were benign per report.

Imaging studies at the time of her presentation to the emergency department revealed abdominopelvic ascites and two sclerotic osseous lesions in the left ischial tuberosity, measuring up to 1.9 cm. No pelvic or abdominal masses were identified. Physical examination revealed a cervical lesion with white, irregular borders at the external os with associated punctate hemorrhage. Cervical biopsies demonstrated at least high grade squamous intraepithelial lesion (HSIL) with inadequate stroma for evaluation of invasion. A follow-up cervical conization revealed no evidence of residual dysplasia, but rather showed a vascular proliferation composed of anastomosing vessels lined by atypical endothelial cells with nuclear hyperchromasia, nuclear tufting, and increased mitotic figures with ill-defined margins. Immunohistochemical studies were performed and demonstrated that the atypical vascular proliferation was negative for pancytokeratin AE1/AE3 and positive for CD31 and ERG, with an increased Ki-67 proliferation index and patchy moderate C-MYC positivity. There was surface denudation and no

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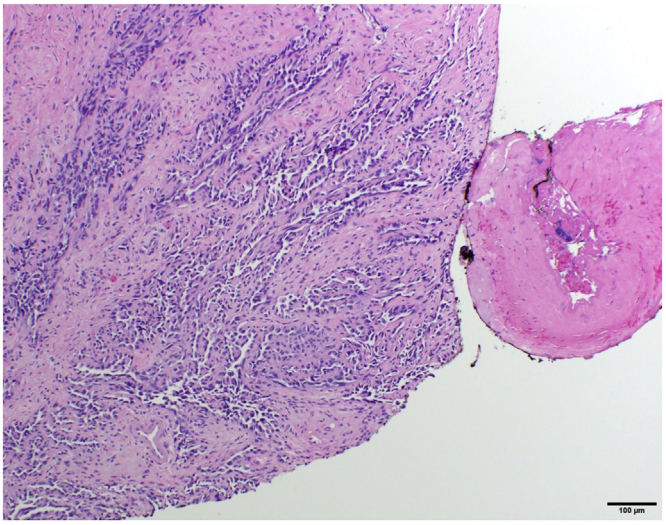


**Fig. 1.** Low power histology of cervical angiosarcoma, showing anastomosing vascular channels with nuclear atypia (100×).

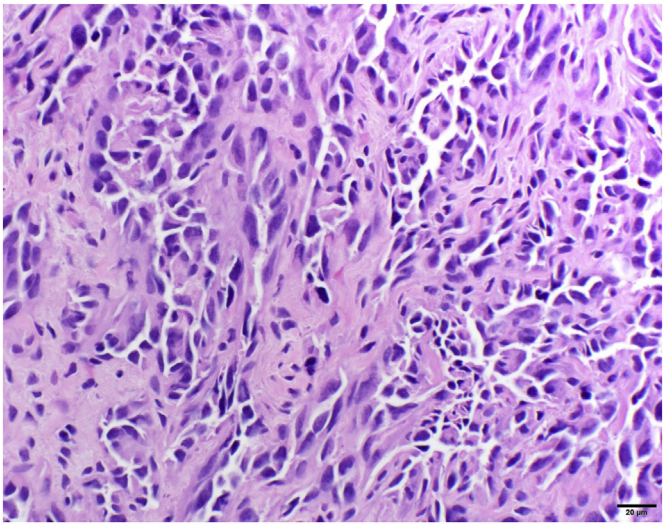


**Fig. 2.** High power histology of cervical angiosarcoma, showing endothelial cells with nuclear atypia, hobnailing, and scattered mitotic figures (400×).

evidence of residual or recurrent squamous cell carcinoma. The case was reviewed in consultation by the Department of Pathology at Johns Hopkins and interpreted as consistent with well-differentiated angiosarcoma, likely radiation-associated (Figs. 1–3).

Post-operatively, the patient underwent staging positron emission tomography (PET) with concurrently acquired computed tomography (CT) which revealed F-18 fluorodeoxyglucose (FDG) avidity of the left cervix, a 2.1 cm FDG-avid left gluteal soft tissue mass, and increased sclerotic osseous lesions in the axial and appendicular skeleton, which were non-FDG-avid on PET scan. Biopsy of the left gluteal mass revealed necrosis and abundant acute inflammation with no diagnostic malignancy, although metastatic disease was favored clinically. Repeat CT approximately 2 weeks later revealed interval growth of the left gluteal mass, increased ascites, omental caking, and bowel changes suspicious for peritoneal disease. A subsequent left ischial biopsy showed benign cortical bone. Given the imaging findings consistent with widely metastatic disease, the patient was started on chemotherapy with gemcitabine and docetaxel as a primary treatment modality. She has had a promising early response to therapy, and remains in treatment at the time of this publication.

## 3. Discussion

Angiosarcoma has a propensity to arise as a cutaneous lesion in sun-exposed areas of the head and neck of older adults, with a marked male predominance (Peng et al., 2014). In addition, there is a well-established association with the development of angiosarcoma in patients who have undergone treatment for breast cancer. Etiologic factors in these cases have been attributed to both ionizing radiation therapy (radiation-associated angiosarcoma) and to chronic lymphedema resulting from surgical mastectomy (Stewart-Treves syndrome). A landmark study using SEER (Surveillance, Epidemiology, and End Result) data indicates that angiosarcomas tend to develop approximately 5–10 years after ionizing radiation in breast cancer patients (Huang and Mackillop, 2001). Subsequent research has confirmed radiotherapy as an independent risk factor, but has also suggested that this phenomenon is not exclusive to breast cancer patients (Huang and Mackillop, 2001).

Although sporadic angiosarcoma has a higher incidence in men, post-radiation angiosarcomas may be more common in women. In a cohort study of over 330,000 Finnish cancer patients, Virtanen et al. found 19 cases of angiosarcoma in a 50 year follow-up period, all occurring in women with primary breast or gynecologic malignancies, despite men comprising 46% of the study population (Virtanen et al., 2007). An ongoing quandary in the treatment of cervical cancer has been the relative survival advantage and morbidity of primary

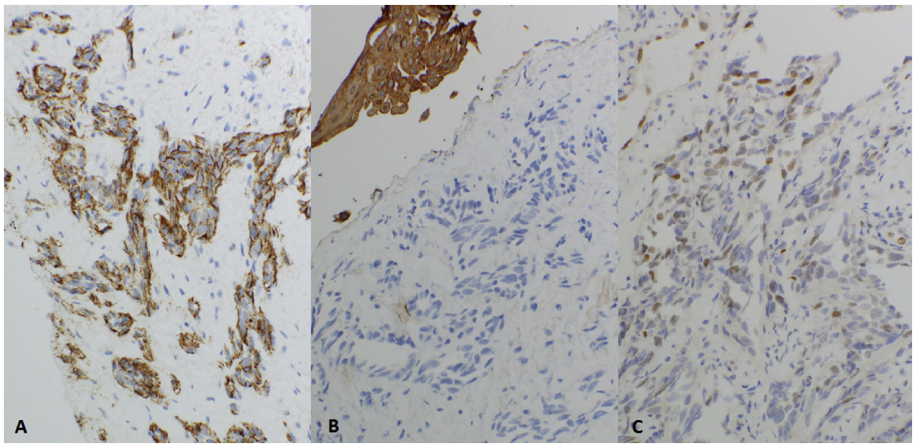


**Fig. 3.** Immunohistochemical stains for cervical angiosarcoma: positive for CD31 (A); negative for pancytokeratin AE1/AE3 with positive internal control (B); patchy moderate positivity for C-MYC (C) (200× for all).

treatment with hysterectomy compared with radiotherapy. In the United States, definitive chemoradiation is now typically preferred over radical surgery for many patients with FIGO stage IB1 and most FIGO stage IIA2 or greater cervical cancers. Brachytherapy is also used in the treatment of endometrial, vaginal, and vulvar cancers. As a result, there may be an increase in the incidence of post-radiation sequelae over time. In six previously reported cases of post-radiation angiosarcomas of the female gynecologic tract, one occurred in the uterine corpus and three in the vagina (the primary site of the remaining two was not reported) (Morgan et al., 1989; Tohya et al., 1991; Chan and SenGupta, 1991; Morrel et al., 1993; Virtanen et al., 2007). The interval from treatment of the primary malignancy to the diagnosis of post-radiation gynecologic angiosarcoma ranged from 6.5 to 21 years (Morgan et al., 1989; Tohya et al., 1991; Chan and SenGupta, 1991; Morrel et al., 1993; Virtanen et al., 2007). With the widespread utilization of radiation and brachytherapy to treat cervical carcinoma and various other malignancies, awareness of such lesions and the ability to recognize them is of paramount importance.

Although angiosarcoma often has a variable histologic appearance that initially suggests a broad differential, our case demonstrated a fairly classic appearance with a proliferation of anastomosing vascular channels lined with plump endothelial cells with nuclear hyperchromasia, nuclear tufting, and scattered mitotic figures. In cases with less characteristic histomorphology, the differential diagnosis may include a variety of vascular lesions (e.g. hemangioma, Kaposi sarcoma), high grade endometrial stromal sarcoma, poorly differentiated/undifferentiated carcinoma, and even melanoma. Relevant immunohistochemical (IHC) stains and cytogenetic/molecular testing may be imperative in establishing the correct diagnosis. In the current case, IHC stains for ERG and CD31 confirmed endothelial origin, and C-MYC positivity supported the histomorphologic impression of a radiation-associated well-differentiated angiosarcoma in this clinical context (Udager et al., 2016).

While many patients present with localized disease, approximately 20–45% have distant metastases at the time of diagnosis, with hematogenous spread to the lungs, lymph nodes, and bones most commonly encountered (Young et al., 2010). Prognostic factors include the size and focality of the neoplasm, as well as margin status in surgically resectable cases. Angiosarcoma of visceral organs (e.g. liver, heart), retroperitoneal sites, and radiation-induced disease had poorer outcomes in some series (Young et al., 2010). Five year overall survival for the rare cases of female genital tract angiosarcomas is reported as 27%, slightly lower than those presenting in other anatomic locations (Kruse et al., 2014; Liu et al., 2016). The standard of care is surgical resection +/− adjuvant chemoradiation therapy in the absence of widely metastatic disease, and chemotherapy in metastatic cases.

## Consent

Written informed consent was obtained from the patient for the publication of this case report.

## Conflict of interest and source of funding

We have no conflict of interest to declare. This work had no specific sources of funding.

## Author contribution

Drs. Betancourt, Randall, and Bookhout drafted and revised the manuscript and prepared the figures. Drs. Kuan-Celarier, West, and Soper also contributed to the manuscript and added additional clinical information. All the authors have read and approved the final manuscript.

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