Case report

Angiosarcoma of the vulva following radiation for colorectal cancer

Madison Meyer a,1, Evan S. Smith a, Mario M. Leitao Jr. a,b,*

a Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York City, NY, USA
b Joan & Sanford I. Weill Medical College of Cornell University, New York, NY, USA

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1. Introduction

Angiosarcomas are aggressive malignant endothelial tumors that originate from the vasculature or lymphatics of any soft tissue. Frequently involving the scalp and arising spontaneously, they can also be associated with chronic lymphedema, exogenous toxin exposure, hereditary familial syndromes, and prior radiotherapy (Young et al., 2010). Angiosarcoma incidence has been on the rise over the past 30 years, but whether this is due to increased use of radiotherapy, improved awareness and histopathological diagnosis, or other reasons is unknown (Young et al., 2010). These tumors are often mistaken for benign lesions upon presentation, leading to diagnosis and treatment delays (Young et al., 2010).

Angiosarcomas of gynecologic origin are exceedingly rare, and treatment plans are formulated based on historical management results along with individualized recommendations. Treatment remains challenging and the prognosis is poor overall, with an estimated 5-year survival of approximately 30% (Kruse et al., 2014). Here we present the case of a patient who developed a radiation-associated angiosarcoma of the vulva.

2. Case

A 65-year-old patient with a history of T2N1 basaloid squamous carcinoma of the anal canal was referred to our center for evaluation in September 2019. The patient’s anal cancer was diagnosed in 2004 and treated with cisplatin, 5-fluorouracil chemotherapy, and radiation therapy to a total dose of 5040 cGy. A recurrence of the anal carcinoma was diagnosed in 2006 and treated with an abdominoperineal resection, and she has been without evidence of anal cancer since that time.

In 2018, the patient presented to her gynecologist with complaints of vulvar itching and erythema. A vulvar biopsy revealed lichen sclerosis, and topical clobetasol propionate cream was prescribed but did not relieve symptoms. Dermatology referral was placed due to ongoing itching and erythema. Culture of the area was positive for Klebsiella pneumoniae and Escherichia faecalis, and she was instructed to continue clobetasol and start topical silver sulfadiazine and a course of oral cefadroxil. A repeat vulvar biopsy was eventually performed in September 2019 and revealed an angiosarcoma, prompting referral to our institution’s Gynecologic Oncology Service.

Upon presentation, we observed a bilaterally thickened, hypertrophied vulva with a 2 cm, nodular, raised, hyperpigmented lesion along the left mid-lateral vulva (Fig. 1). Pathology slides from the September 2019 biopsy were reviewed, and our pathologists concurred with the diagnosis of angiosarcoma. Immunostains were positive for CD31 with an elevated Ki67 proliferation index and negative for pancytokeratin (AE1/AE3). Immunohistochemistry (IHC) for C-MYC showed expression in the neoplastic cells. Magnetic resonance imaging (MRI) of the pelvis showed no focal suspicious vulvar lesion and no pelvic metastases, and a computed tomography (CT) scan of the chest, abdomen, and pelvis showed no radiologic evidence of distant metastases. In November 2019, the patient underwent a radical bilateral vulvectomy with a resulting 15 cm × 22 cm defect in the pelvis. Multiple peripheral biopsies obtained intraoperatively were sent for frozen pathology and resulted positive for malignancy, prompting additional resections to clear the sarcoma. While clitoris-sparing surgery was planned...
if a negative margin could be obtained, it too required removal. (Fig. 2) At case-conclusion, there was no visibly abnormal tissue remaining. The plastic surgery service reconstructed the pelvis with bilateral, pedicled thigh profunda artery perforator flaps. (Fig. 3) Total estimated blood loss for the entire procedure was 100 mL.

The tumor specimen and blood were submitted for somatic and germline mutation profiling via our institution’s Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) (Cheng et al., 2015) which identifies somatic mutations in a 468-gene panel and germline mutations in an 88-gene panel. Somatic mutations were found in EPHA7 (X55_splice:c.163-2A > C) and CIC (R1171Q:c.3512G > A), and a 1.7 fold copy-number gain of MAPK1 at 22q11.22 was observed; no germline mutations were identified.

The patient recovered well and was discharged on postoperative day three. The final pathology report described a high-grade angiosarcoma with multiple positive peripheral margins. There were no remaining visible lesions at the completion of resection or at initial postoperative visit. The risk of microscopic residual disease was discussed, and she was referred to our Sarcoma Medical Oncology group for additional treatment recommendations. Ultimately, expectant management was advised with close clinical and radiological surveillance. Exams and imaging, including MRI and positron emission tomography (PET) have been reassuring to date, without evidence of disease at 13 months post-operation.

3. Discussion

Angiosarcomas can occur spontaneously or secondary to chronic lymphedema, radiation, toxins (e.g. vinyl chloride, arsenic, anabolic steroids, thorium dioxide, and foreign bodies), and familial syndromes (e.g. NF-1, BRCA1, BRCA2, Maffucci Syndrome, and Klippel-Trenaunay Syndrome). Along with etiologic differentiations, they may be further subdivided into five subtypes: cutaneous, lymphedema-associated, radiation-induced, primary breast, and soft-tissue angiosarcoma (Young et al., 2010).

Radiation-induced angiosarcomas are often mistaken for radiation-induced skin changes following radiotherapy (Sanz et al., 2005). The diagnostic criteria for radiation-induced sarcoma include development within a field of radiation, latency of 3–4 years between radiation and diagnosis, and a histological difference from the primary cancer (Arlen et al., 1971). MYC amplification has also been shown to be an early but necessary pathogenic event for radiation-induced angiosarcomas, promoting dysregulated cellular proliferation by passing inappropriately from the G1 phase to S phase (Guo et al., 2011). Along with the timing, location, and histology of our patient’s tumor, the C-MYC IHC supports the diagnosis of a radiation-induced angiosarcoma.

Angiosarcomas rarely affect the female genital tract. A 2014 literature review by Kruse et al demonstrated 52 patients with primary angiosarcomas of the female genital tract. Twenty-nine had angiosarcoma of the ovary, 18 patients had angiosarcoma of the uterus, two patients had angiosarcoma of the vagina, and two had angiosarcoma of

Fig. 1. Affected vulva prior to planned procedure with surgical markings outlining planned resection margins.

Fig. 2. Pelvis post-radical vulvectomy with clitorectomy.

Fig. 3. Healed, reconstructed vulva using bilateral, pedicled thigh profunda artery perforator flaps. Image captured at three months post-operation.
the vulva. Only one of the patients with a vulvar angiosarcoma includes treatment and follow-up data; the tumor was treated with wide excision and the patient died of disease at 48 months post-operation (Kruse et al., 2014). In addition to this review, we have found only three other cases of vulvar angiosarcoma in the medical literature. Guirguis et al describe an angiosarcoma of the Mons that developed four years after vulvar radiation for a squamous carcinoma; the patient was treated with surgical resection and recurred 6 months post-operation (Guirguis et al., 2007). Sheinis et al report a likely spontaneous vulvar angiosarcoma, which was resected via vulvectomy with bilateral inguinal lymphadenectomy but recurred within a month of the patient’s surgery; at the time of their report she was 24 months post-operation but receiving palliative care for widely metastatic disease (Sheinis et al., 2016). Yost et al describe an angiosarcoma of the vulva that developed in a patient at age 90, five years after pelvic radiation for an endometrial cancer. Of note, the patient also had post-treatment lymphedema, a second risk factor for angiosarcoma. She declined further therapy (Yost et al., 2017). Due to the invasive and multifocal nature of the disease, the treatment of choice for localized angiosarcoma is radical surgery with wide margins. In addition to surgical excision, adjuvant radiation therapy with a large dose and wide treatment field may be recommended due to the high likelihood of local recurrence, although additional radiation therapy is avoided in radiation-induced angiosarcomas (Young et al., 2010). For those who unfortunately present with or develop a recurrence as metastatic disease, there are several cytotoxic and targeted therapies including anthracyclines, taxanes, VEGF inhibitors, and tyrosine kinase inhibitors. (Florou and Wilky, 2018) However, metastatic angiosarcomas are highly aggressive, incurable, and often fatal. Our patient’s postoperative course has been promising thus far, supporting an aggressive, radical surgical approach to newly diagnosed vulvar angiosarcomas.

4. Consent
Informed consent was obtained from the patient for publication of this case report and accompanying images.

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Disclosures
MML is a consultant for Intuitive Surgical Inc., outside the submitted work.

CRediT authorship contribution statement

Madison Meyer: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Evan S. Smith: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Mario M. Leitao Jr.: Conceptualization, Formal analysis, Supervision, Writing - review & editing.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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