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Case report

Superior Vena Cava Syndrome associated with recurrent uterine adenosarcoma

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1. Introduction

Sarcomas represent approximately 5–8% of all uterine cancers, and these are comprised of high grade lesions such as leiomyosarcoma and low grade lesions such as endometrial stromal sarcoma/adenosarcoma (McCluggage, 2010). Adenosarcoma is a rare tumor characterized by a benign epithelial component mixed with malignant stroma. Approach to the treatment of adenosarcomas is typically driven by certain risk factors, specifically the presence of lymphovascular space invasion and sarcomatous overgrowth. Adenosarcomas with low-risk features are often treated with surgery alone as the recurrence rate without high-risk histologic features is quite low, with one retrospective case series reporting a recurrence rate of 22% among stage I patients without sarcomatous overgrowth as compared to 77% with sarcomatous overgrowth (Carroll et al., 2014). Sarcomatous overgrowth can occur in up to 54% of patients and has been associated with a higher risk of recurrence and overall poorer prognosis, and therefore some of these patients receive adjuvant therapy (Carroll et al., 2014; Verschraegen et al., 1998). Classically the pattern of spread of sarcomas is hematogenous. Uterine sarcomas generally follow this paradigm, as the vast majority of adenosarcomas that recur do so locally in the pelvis, contrasted with uterine carcinomas which are more likely to spread via lymphatic metastasis (McCluggage, 2010). Local metastasis/recurrence in the pelvis is the most common form of spread for all uterine cancers, but in rare circumstances when there is distant spread, uterine cancers tend to follow this aforementioned sarcoma/carcinoma pattern.

Superior vena cava (SVC) Syndrome is caused by obstruction of the SVC that most commonly causes swelling of the areas drained by the SVC (head, neck, upper extremities), shortness of breath, and coughing. SVC Syndrome is commonly associated with malignancy, typically bronchogenic carcinoma or lymphoma, and can result either from external compression of the SVC or from direct extension/invasion of a mass. Malignant SVC Syndrome can be treated with systemic treatment versus local treatment with stenting or radiation, usually with some level of symptomatic relief. One case series reported that up to 83% of patients receiving radiation therapy for all-cause malignant SVC Syndrome had symptomatic improvement (Armstrong et al., 1987).

2. Case report

A 52-year-old G1P0010 presented to her primary provider with menorrhagia. She had previously been on OCPs for many years and after cessation noted heavy bleeding and dyspareunia. She underwent a hysteroscopy with dilation and curettage and final pathology of the currettings revealed adenosarcoma with up to five mitoses per ten high-power fields. She continued to have vaginal bleeding, was started on

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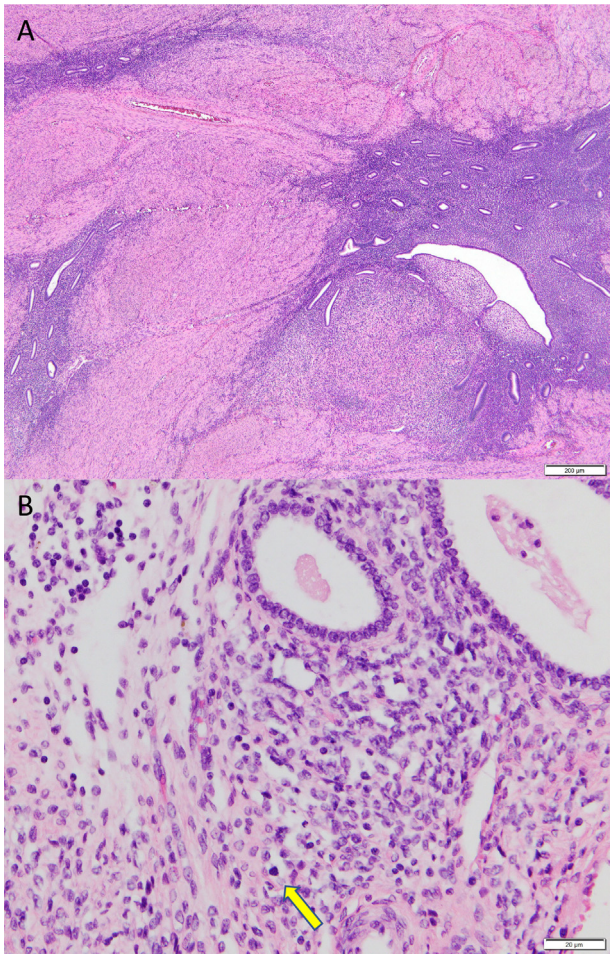

Fig. 1. Microphotography of uterine resection specimen. (A) Hematoxylin and eosin (H&E) stain shows the tumor with phyllodiform architecture involving existing adenomyosis (40×). (B) High power field image shows benign glandular structure with periglandular stromal condensation of malignant cells with occasional mitotic figures (arrow), involving an endometrial polyp (400×). Those features fulfill the diagnostic criteria of adenosarcoma.

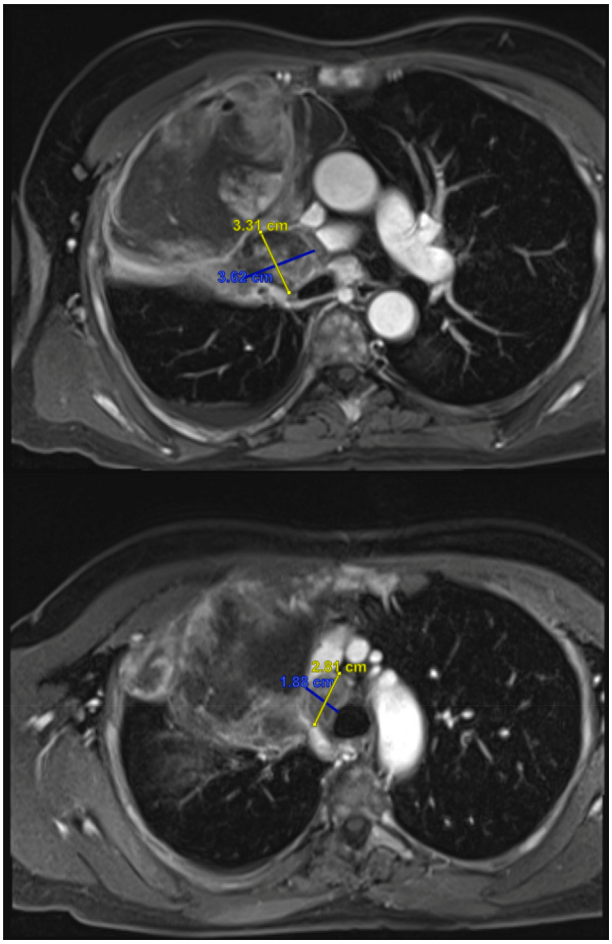

Fig. 2. MR Images of Metastatic Disease. Axial MR images of large necrotic mass in right upper lobe and paratracheal/hilar lymphadenopathy with associated narrowing of the superior vena cava.

progesterone suppression, and was referred to gynecologic oncology. Her past medical history was unremarkable. She had no past surgical history. She was up-to-date on age-appropriate cancer screening. She had no family history of any cancers.

Following consultation with a gynecologic oncologist, she underwent a total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLH/BSO). Gross examination of the specimen revealed a 3 cm exophytic mass involving the anterior and posterior endometrium. Histopathological examination revealed a tumor with phyllodiform architecture and periglandular stromal condensation with no sarcomatous overgrowth. The tumor involved adenomyosis and an endometrial polyp. Up to three mitoses per ten high-power fields were identified. No necrosis was present. Those features fulfilled the diagnosis of residual uterine adenosarcoma without high grade features (Fig. 1). There was uninvolved adenomyosis extending throughout the myometrium to within 1 mm of the serosa. Less than 50% (up to 30%) of the depth of adenomyosis was involved by the tumor; however, there was no myometrial involvement. Although there is some data that invasion of adenomyosis is associated with myometrial invasion in other gynecologic malignancies, there was no myometrial involvement by the involved adenomyosis in this patient's specimen (Ismiil et al., 2007). Pelvic washings were negative for malignancy. She was therefore Stage IA, did not receive adjuvant therapy, and was surveilled closely with office visits and exams every six months.

Two years after her TLH/BSO, she presented with rib pain, shortness of breath, and fatigue and was found to have a large 10 cm right upper lobe lung mass and diffuse bony metastases (Fig. 2). Biopsy of the lung mass revealed a malignant spindled and epithelial cell neoplasm, consistent with metastasis of her Müllerian adenosarcoma (Fig. 3). Interestingly, next generation sequencing of this patient's metastasis revealed an NRAS p.Q61K mutation and three DICER1 variants – p.D1709N, p.E1316delinsVMDL, and c.5095 + 6G > A. The presence of at least two hits in DICER1, including within the RNAse IIIb domain (codon 1709), is characteristic of tumors associated with defects in this gene (Bean et al., 2019).

Notably, she had extensive paratracheal and hilar lymphadenopathy that caused severe narrowing of the SVC. She had associated respiratory collapse requiring intubation and upper extremity vascular congestion consistent with SVC Syndrome. Given concern for SVC syndrome, she underwent SVC stenting and palliative radiation to the lung mass/mediastinum (20 Gy in five fractions). She had malignant fracture of a femoral bony metastasis that was biopsied and also shown to be consistent with metastatic Müllerian adenosarcoma. Given the patient's poor prognosis and performance status, she was offered liposomal doxorubicin due to its favorable side effect profile which she declined in favor of supportive care, ultimately dying peacefully in the hospital with palliative care two months after presentation.

3. Discussion

This case is of particular interest because of the abnormal pattern of

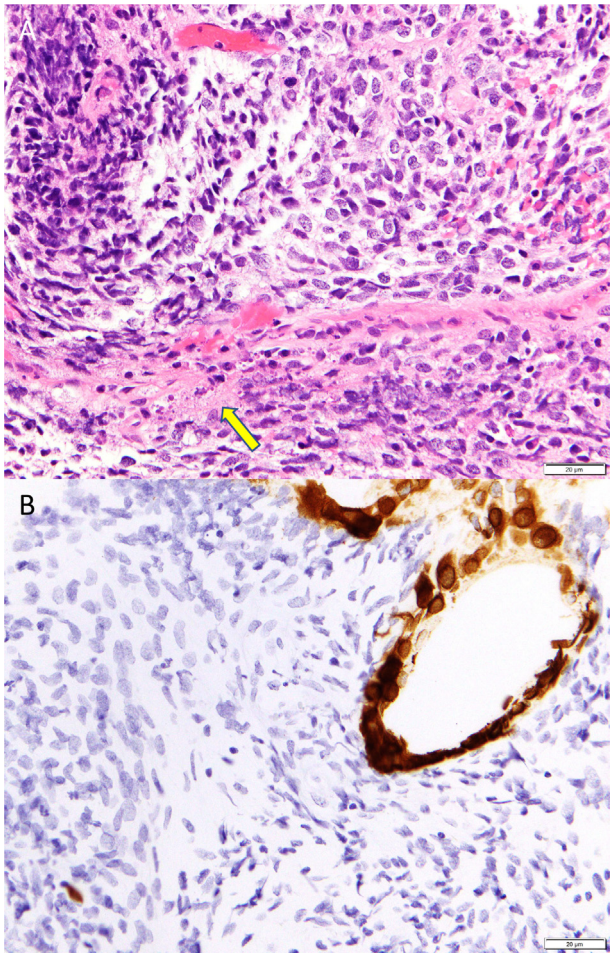

Fig. 3. Microphotography of endobronchial biopsy. (A) H&E stain shows a malignant spindled and epithelial cell neoplasm with increased tumor cell pleomorphism and focal necrosis (arrow), consistent with metastasis from patient's known Müllerian adenosarcoma (400×). (B) Immunohistochemistry image of AE1/AE3 keratin stain highlights the glandular component of the adenosarcoma, whereas the sarcomatoid component is negative for keratin staining (400×).

metastasis and the resultant SVC syndrome. The reasons sarcomas typically favor hematogenous metastasis while carcinomas favor lymphatic metastasis are incompletely understood. Multiple etiologies of this paradigm have been proposed, and the role of the tumor microenvironment and permeability of blood vessel versus lympatic tissue have been investigated, but a clear explanation for this behavior is not known. The reported case is interesting due to the pattern of spread—as previously discussed, adenosarcoma generally has low metastatic potential and when it recurs/invades, it tends to do so locally. In this case of adenosarcoma, the tumor metastasized not only distantly but also via lymphatic spread.

Next generation sequencing of this patient's metastasis revealed an NRAS p.Q61K mutation and three *DICER1* variants – p.D1709N, p.E1316delinsVMDL, and c.5095 + 6G > A. The presence of at least two hits in *DICER1,* including within the RNAse IIIb domain (codon 1709), is characteristic of tumors associated with defects in this gene (Bean et al., 2019). In one series of uterine adenosarcomas, 42% of tumors had *DICER1* mutations, but none were germline (Bean et al., 2019); however, germline variants have been reported (Mullen et al., 2017). Further work is needed to understand how both germline and somatic *DICER1* mutations may contribute to the development and clinical course of uterine adenosarcomas and if the mutation presents any potential therapeutic targets.

Furthermore, this patient's recurrence with SVC Syndrome is extraordinarily uncommon for gynecologic cancers in general. There have been reported cases of SVC Syndrome in the gynecologic oncology literature, with most cases arising from metastatic cervical squamous cell carcinoma (Charles and Savage, 1980; Biswal et al., 1995). Two other cases have been reported, one case arising from endometrial carcinoma and the other arising from uterine leiomyosarcoma (Puleo et al., 1986). To the authors knowledge, there are no reported cases of a uterine adenosarcoma with this presentation.

The dramatic presentation and short survival of the patient in this case underscores the need for risk stratification and further understanding of risk factors in uterine adenosarcoma. As discussed previously, sarcomatous overgrowth is the best studied prognostic indicator in terms of ability to predict recurrence risk and therefore guide adjuvant therapy decisions. This patient's tumor did not contain sarcomatous overgrowth, and furthermore, the metastatic disease did not exhibit overt features of high grade transformation, although the limited size of the metastatic biopsies precluded comprehensive characterization of the pathologic features. This case serves to highlight an abnormal pattern of recurrence for what is usually a low-risk malignancy. Future research into the prognostic value of invasion of adenomyosis could prove useful in further elucidating patients who may be at high risk of adverse outcomes. Further research is needed to determine which patients with uterine adenosarcoma are at risk of recurrence, metastasis, and morbidity to further risk stratify which patients may benefit from adjuvant therapy after definitive surgery.

Author contributions

Mackenzie W. Sullivan was the primary author and was responsible for writing and revising the original manuscript.

Allison Gockley and Colleen Feltmate were responsible for reviewing and editing the manuscript.

Ying-Chun Lo and Lynette M. Sholl were responsible for reviewing and editing the pathology content of the manuscript and contributed Figs. 1 and 3.

Suzanne George was responsible for reviewing the sarcoma content of the manuscript.

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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