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Case report

Epithelioid angiosarcoma arising in a uterine leiomyoma with associated elevated CA-125: A case report

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ABSTRACT

We describe the case of a 67 year old female with longstanding uterine leiomyomas who presented with fatigue, weight loss, elevated CA-125 and an enlarging mass arising from the posterior uterine fundus. Histologic sections of the mass contained a leiomyoma with interspersed foci of malignant epithelioid cells forming anastomosing vascular channels. The neoplastic cells were diffusely positive for CD31 and FLI1, supporting the morphologic impression of epithelioid angiosarcoma. Few cases of epithelioid angiosarcoma arising within a leiomyoma have been described. In this report we discuss this association and describe its relation with elevated CA-125.

1. Introduction

Angiosarcomas are aggressive neoplasms of endothelial origin which typically arise in the skin or superficial soft tissues of elderly patients and account for approximately 4% of sarcomas (Toro et al., 2006). Although rare, within the gynecologic tract, angiosarcoma has been described to arise from the cervix, ovary, vulva, vagina and uterus (Kruse et al., 2014). We present the case of a 67 year old female who developed epithelioid angiosarcoma within a pre-existing uterine leiomyoma. To the best of our knowledge, this is only the third time this association has been reported and the association with a significantly elevated CA-125 has not previously been described.

2. Case report

A 67 year old G0 woman with a history of uterine leiomyomas diagnosed in adolescence presented to her primary care practitioner with a chief complaint of fatigue and unintentional weight loss. She reported scant bloody vaginal discharge but denied abdominal distension, pain, or changes in her bowel and bladder habits. The patient had been in menopause since age 53 and, at that time, was told her uterus was enlarged due to leiomyomas to that of 3–4 months' gestation. She had no other relevant medical or surgical history. Upon examination the patient had a BMI of 16.5 kg/m^2 and examination of her abdomen revealed a firm mass arising from the pelvis and extending above the umbilicus, approximately 5–6 cm below the xiphoid process. A pelvic exam was performed, which was significant for a small amount of blood in the vaginal vault, but she was unable to tolerate further exam. Endometrial sampling was precluded due to severe distortion of anatomy by the large mass. Due to her symptoms and physical examination findings the patient underwent laboratory evaluation and computed tomography (CT) scans of the abdomen and pelvis. Laboratory studies were significant for anemia (hemoglobin 8.2 g/dL, hematocrit 26.2%) as well as an elevated CA-125 (237.5 U/mL) and CT of the abdomen and pelvis (Fig. 1) revealed a 21 × 18 × 15 cm heterogeneous and septated mixed density pelvic mass. It was unclear whether the origin of the mass was uterine or ovarian, however, the mass contained a large area of calcification suggestive of a calcified leiomyoma. Subsequent abdominal and pelvic magnetic resonance imagining (MRI) studies again showed a large heterogeneous pelvic mass measuring 24 × 20 × 12 cm with calcification noted in the right lateral aspect. The uterus and ovaries could not be visualized and no gross evidence of extra-uterine disease was identified. A CT of her thorax revealed three pulmonary nodules measuring up to 0.7 cm in maximal dimension however these were felt to be non-specific. Evaluation by a gynecologic oncologist was suspicious for possible uterine sarcoma, and surgical resection was recommended for definitive diagnosis and management. The patient therefore underwent subsequent exploratory laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy. Intraoperative findings were significant for a large mass confirmed to be arising from the posterior fundus of the uterus with a smooth external contour. The bilateral ovaries appeared atrophic without adnexal masses and there was no evidence of extrauterine disease or adenopathy. The enlarged uterus and adnexa

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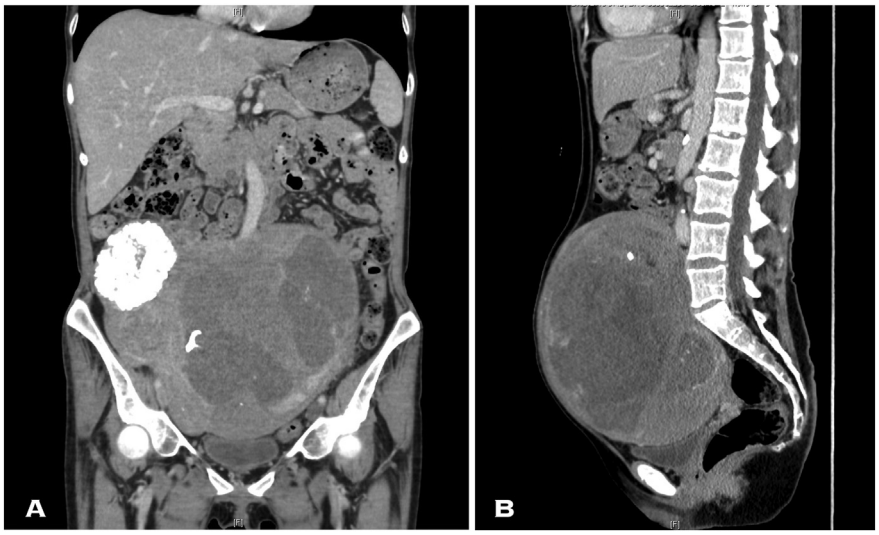

Fig. 1. Abdominal and pelvis computed tomography (CT) images. A) Coronal and B) sagittal views demonstrating a heterogeneous and septated mixed density pelvic mass with an area of calcification in the right lateral aspect.

were removed on bloc without morcellation of the specimen. Intraoperative frozen section was consistent with a hemorrhagic degenerating leiomyoma without evidence of malignancy.

3. Pathologic findings

The uterus measured 25 cm in maximal dimension and weighted 3901 g. The myometrium was distended by three well-circumscribed intramural masses, the largest of which measured 17 cm and contained areas of hemorrhage, necrosis and calcification. The intervening myometrium, endometrium, bilateral ovaries and fallopian tubes were grossly unremarkable.

Histologic sections (Fig. 2) of the largest intramural mass were composed predominantly of spindled cells arranged in a fascicular pattern with areas of hyalinization and calcification, consistent with a longstanding leiomyoma. Interspersed throughout the leiomyoma and associated vessel lumens there was a multifocal and distinct population of pleomorphic and epithelioid cells which formed sheets and atypical anastomosing channels containing red blood cells. Abundant mitotic activity and necrotic debris were also present. The epithelioid neoplastic cells were not present within the endometrium or myometrium which was sampled outside of the leiomyoma. Immunohistochemical

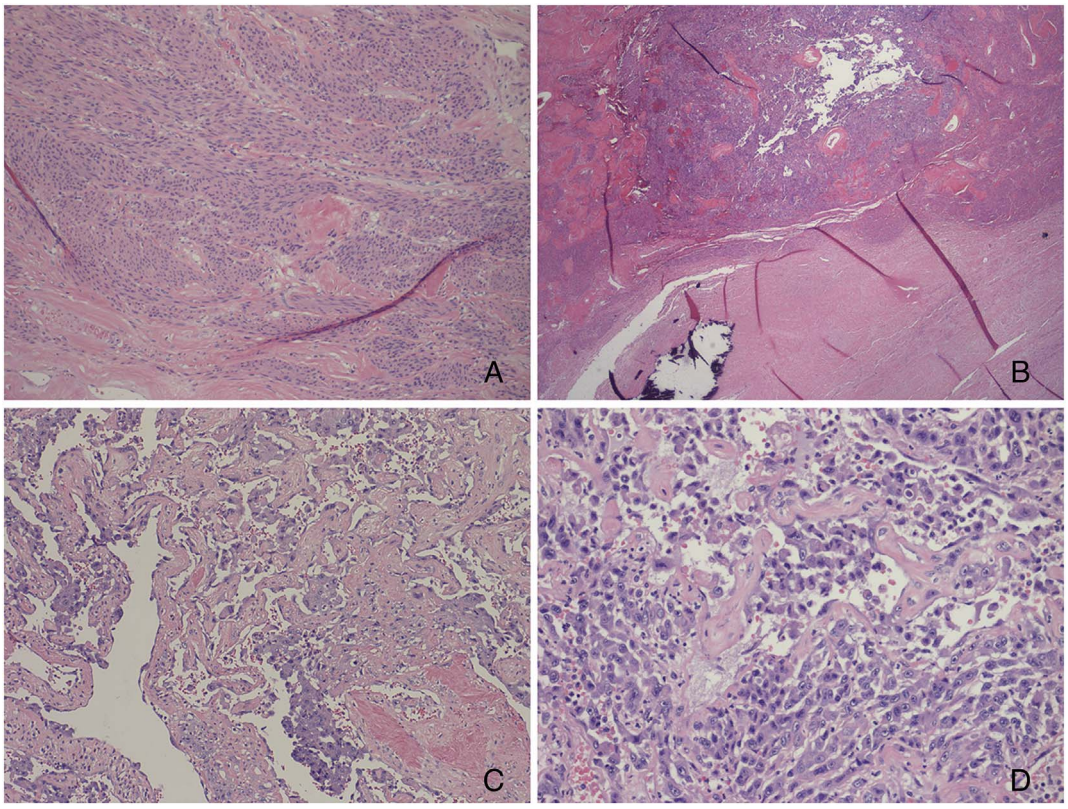

Fig. 2. Histologic features of largest intramural uterine mass. A) Bundles of smooth muscle with conventional appearance of leiomyoma, B) low-powered view (40 ×) of neoplastic cells interspersed amongst bundles of smooth muscle. C–D) Anastomosing vascular channels lined by enlarged and atypical epithelioid cells.

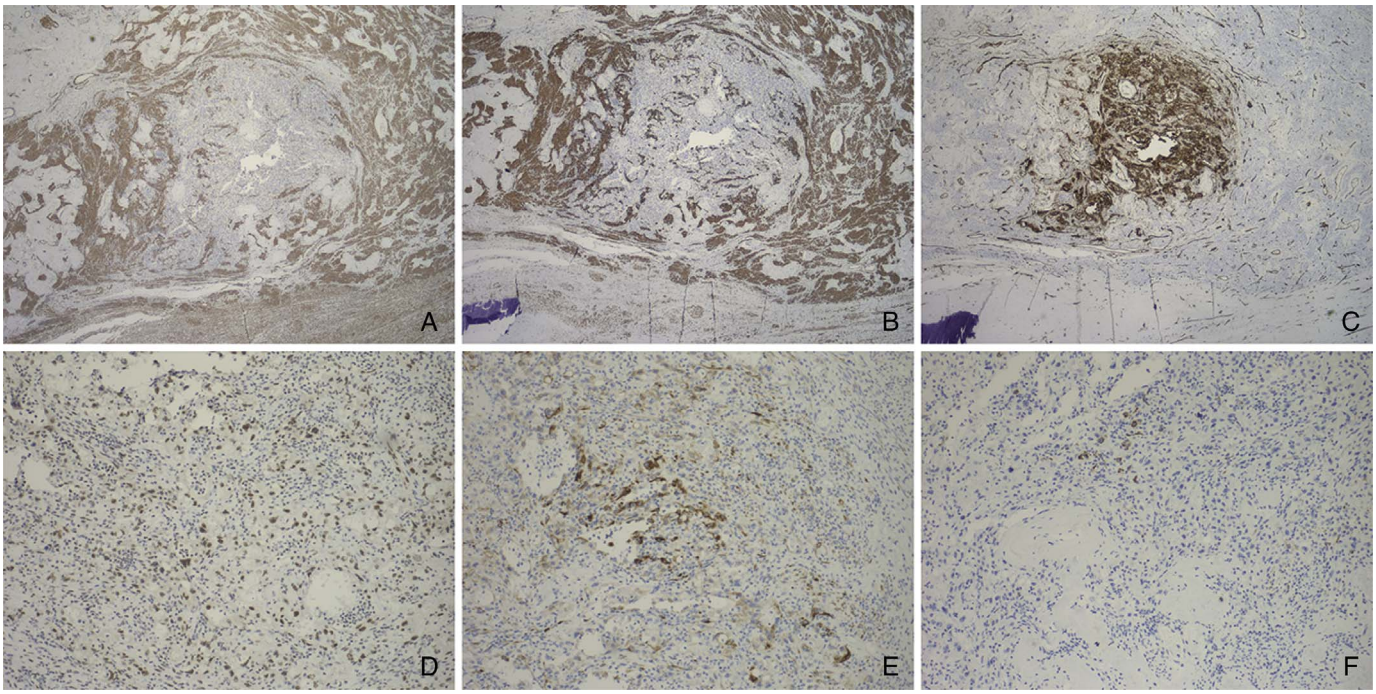

Fig. 3. Immunohistochemical features (all photos at 40 ×). A) Smooth muscle actin and B) desmin highlight surrounding leiomyoma. Epithelioid angiosarcoma cells positive for C) CD31, D) FLI1, E) Oscar cytokeratin and F) CAM5.2.

studies revealed that the neoplastic cells were diffusely positive for CD31 and FLI1 and had focal staining for CAM 5.2 and Oscar cytokeratin (Fig. 3). They were negative for pancytokeratin, EMA, desmin, actin, S100 and CD34. Overall the morphologic and immunohistochemical features were supportive of a neoplasm of endothelial origin and a diagnosis of epithelioid angiosarcoma was rendered. The permanent sections of the tissue sampled during intraoperative frozen section were confirmed to be negative for angiosarcoma.

4. Outcome and follow-up

Given the neoplasm's rare and aggressive histology, a referral was placed for the patient to see a medical oncologist specializing in sarcomas for recommendations regarding adjuvant therapy. Due to social issues, however the patient was unable to attend her first scheduled visit. Soon thereafter she began experiencing worsening dyspnea and was eventually admitted to hospital secondary to her deteriorating respiratory status. Thoracic imaging revealed multiple new multifocal bilateral nodular opacities and ground glass lesions that were initially concerning for an infectious etiology with reactive lymphadenopathy. The pre-existing bilateral pulmonary nodules were unchanged in size. Over the next two weeks, the numerous bilateral pulmonary opacities increased in size despite treatment with antibiotics, and she developed a new adrenal nodule concerning for metastases. She continued to develop new pulmonary nodules, and a lung nodule biopsy confirmed metastatic angiosarcoma. Due to her rapidly deteriorating clinical condition she was unable to tolerate any adjuvant therapy and died approximately two months following diagnosis.

5. Discussion

Uterine angiosarcoma is a rare and aggressive neoplasm with approximately only 20 cases described in the last 40 years (Suzuki et al., 2014; Cardinale et al., 2008; Konishi et al., 2007; Medina et al., 2001; Schammel and Tavassoli, 1998; Drachenberg et al., 1994; Tallini et al., 1993; Ongkasuwan et al., 1982). While angiosarcoma can be composed of anastomosing vascular channels with intraluminal papillary projections, the neoplastic endothelial cells may have a predominantly epithelioid appearance (epithelioid angiosarcoma). Women who develop uterine angiosarcoma are most often postmenopausal, and typically present with vaginal bleeding and weight loss. Pelvic examination reveals an enlarged uterus presenting as a pelvic mass in almost all cases. Grossly, the majority of cases have been described as spongy and hemorrhagic masses which fill the uterine cavity and, by microscopy, diffusely infiltrate the myometrium (Suzuki et al., 2014; Cardinale et al., 2008; Konishi et al., 2007). In a minority of cases, the neoplasm is described as well circumscribed (Cardinale et al., 2008; Medina et al., 2001; Schammel and Tavassoli, 1998; Ongkasuwan et al., 1982).

While few case reports are suggestive of angiosarcoma arising in association with uterine smooth muscle proliferation (Medina et al., 2001; Schammel and Tavassoli, 1998), epithelioid angiosarcoma specifically arising in association with uterine leiomyomas has been previously described only twice. Tallini et al. (Tallini et al., 1993) described a 65 year old patient who presented with vaginal bleeding. Hysterectomy and bilateral salpingo-oophorectomy revealed multiple uterine leiomyomas measuring up to 30 cm as well as multiple other extrauterine leiomyomas attached by stalks to the parametrium. The majority of leiomyomas contained epithelioid angiosarcoma with cells that were positive for CD31, CD34, Factor VIII, CAM 5.2 and AE1/AE3 and no neoplasm was identified in the intervening myometrium. The patient initially declined adjuvant treatment but 2 months post-operatively, had tumor recurrences in the pelvis and upper abdominal cavity. Despite adjuvant chemotherapy she developed brain and bone metastases and died of from this disease 7 months after the initial diagnosis.

Similarly, Drachenberg et al. (1994) reported the case of a 58 year old woman with a history of severe vaginal bleeding. Hysterectomy and bilateral salpingo-oophorectomy revealed an enlarged uterus with multiple leiomyomas measuring up to 12 cm in diameter. The largest leiomyoma contained epithelioid angiosarcoma with cells which were positive for factor VIII and had ultrastructural demonstration of Weibel-Palade bodies. The patient received adjuvant radiation and chemotherapy but died 2 months after diagnosis with diffuse abdominal and vaginal recurrences. It is unknown whether angiosarcoma was identified in the intervening myometrium or whether the patient developed distant metastases.

Similar to previously described cases, the patient herein described presented with weight loss, vaginal bleeding, anemia and a pelvic mass. A notable finding in this case however, is that the patient had an elevated CA-125 of 237.5 U/mL. Elevated CA-125 has been described in association with uterine leiomyomas (Dong et al., 2015) as well as sarcomas including leiomyosarcoma, stromal sarcoma and rhabdomyosarcoma (Duk et al., 1994; Yilmaz et al., 2009; Menczer et al., 2014; Holcomb et al., 1999). Authors have postulated that this elevation is due to reactive mesothelial cells, and there have been conflicting reports as to whether CA-125 level predicts extrauterine disease involvement and higher disease stage (Duk et al., 1994; Yilmaz et al., 2009). We acknowledge that, in this case, it is difficult to determine whether the patient's CA-125 level was elevated due to leiomyomas or whether the admixed angiosarcoma was also responsible. It is possible that the growth of angiosarcoma within the patient's leiomyoma also caused a resultant increase in the size of the leiomyoma (and hence, an elevated CA-125). The two previous cases of angiosarcoma arising within leiomyomas did not have CA-125 levels reported and, although a slight elevation of CA-125 (46 U/mL) has been described in association with uterine angiosarcoma (Konishi et al., 2007) to the best of our knowledge, a level of this magnitude has never been described.

While the patient herein described was not well enough to receive adjuvant therapy, similarly to the previous cases, she died several months after diagnosis. This report confirms the aggressive and rapid clinical course of this neoplasm and highlights the need for more effective treatment modalities in the future.

In summary, we report the case of an epithelioid angiosarcoma arising in an intramural uterine leiomyoma. This unique case is the first to describe a significantly elevated CA-125 in association with a uterine angiosarcoma and further contributes to our knowledge of a rare gynecologic neoplasm.

Consent

Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Institutional review board review

Institutional Review Board (IRB) consent was waived as per institution policy.

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Conflict of interest statement

The authors have no conflict of interest.

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