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Case report

An unusual case of uterine PEComa presenting with disseminated intravascular coagulation

Rodger Rothenberger[a,*], Amanda Jackson[a], Ady Kendler[b], Thomas Herzog[a], Caroline Billingsley[a]

[a] Department of Obstetrics and Gynecology, Division of Gynecology Oncology, University of Cincinnati, 231 Albert Sabin Way, Academic Health Center, PO Box 670526, Cincinnati, OH 45267-0526, United States of America

[b] Department of Pathology, University of Cincinnati, 234 Goodman Street, Cincinnati, OH 45219, United States of America

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ABSTRACT

Perivascular epithelioid cell neoplasms (PEComas) are mesenchymal neoplasms originating from the perivascular epithelioid cell (PEC) line. The World Health Organization (WHO) further defines PEComa as "a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells". Gynecologic PEComas account for approximately ¼ of the PEComa cases reported in the literature and are histologically characterized by stromal hyalinization with complete or partial circumscription with hyaline background and diffuse, small vessel vascularity (Musella et al., 2015). Uterine PEComas typically present with vaginal bleeding and/or a uterine mass, are managed surgically with resection, and can be followed by adjuvant treatment if indicated based on pathologic risk factors for aggression. Adjuvant therapy is not standardized given the rarity of these tumors, and can include chemotherapy, radiation, targeted therapy (mTOR inhibitors due to common gene mutations and a hypothesized pathophysiology of this neoplasm) and/or hormones. In this case report, we describe an unusual presentation for a uterine PEComa in a woman initially complaining of worsening cutaneous bruising and petechiae, found to be in florid disseminated intravascular coagulation (DIC) without a clear etiology. Ultimately her extensive hematology evaluation only found a large uterine mass that appeared to be a 9 cm fibroid. She underwent hysterectomy following recovery from her DIC, and was diagnosed with a large uterine PEComa.

1. Case report

A 61-year-old woman presented to the emergency department with diffuse petechaie throughout body as well as mucosal and vaginal bleeding. She was found to have severe thrombocytopenia (3000/μl) and disseminated intravascular coagulation (DIC) of unknown etiology. She was transfused platelets urgently with subsequent infusion of fresh frozen plasma and cryoprecipitate based on evidence of coagulopathy, followed by intravenous immunoglobulinand high dose steroids and an outpatient oral steroid taper for suspected immune thrombocytopenic purpura (ITP) based on a thorough evaluation by hematology. The patient underwent a CT abdomen and pelvis that revealed a fibroid uterus with a dominant fibroid measuring up to 9 × 9 cm causing compression of the posterior bladder wall with bilateral hydronephrosis and hydroureter. The patient was discharged on hospital day 7 for outpatient follow-up, however four days after discharge the patient was diagnosed with bilateral deep venous thromboses (DVTs). She was started on oral therapeutic anticoagulation. An endometrial biopsy performed after resolution of the DIC revealed a uterine PEComa without evidence of mitoses, necrosis, or nuclear atypia. A PET CT revealed a large centrally necrotic uterine mass with abnormal FDG (maximum SUV 7.1) uptake about its periphery, concerning for malignancy (Fig. 1).

She underwent a robotic hysterectomy and bilateral salpingo-oophorectomy with no evidence of extra-uterine disease grossly. Despite its enlarged size, the uterus was boggy and easily delivered vaginally in a bag without intra-abdominal spillage. Pathology revealed the tumor to be six centimeters in size, with areas of necrosis, positive lymphovascular infiltration and an infiltrative edge. Given these findings, the patient was considered at increased risk for recurrence and was offered adjuvant therapy. Adjuvant chemotherapy was not elected by the patient and, instead, treatment with an aromatase inhibitor (letrozole 2.5 mg daily) secondary to the tumor's hormone receptor positivity was undertaken. Per NCCN guidelines the patient will undergo surveillance

* Corresponding author at: Department of Obstetrics & Gynecology, University of Cincinnati, 231 Albert Sabin Way, Academic Health Center, PO Box 670526, Cincinnati, Ohio 45267-0526, United States of America.
E-mail address: rothenrr@ucmail.uc.edu (R. Rothenberger).

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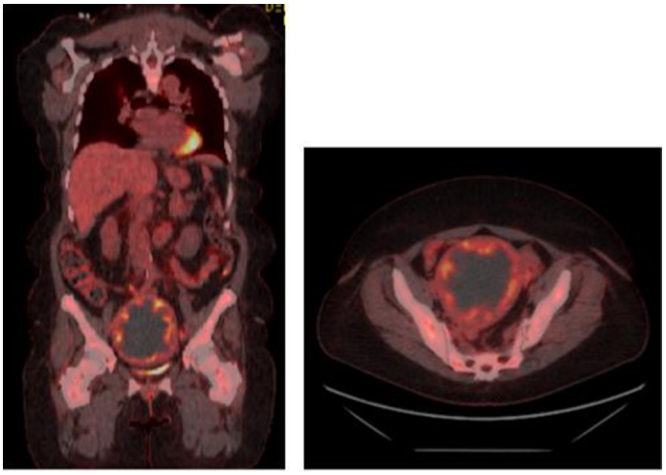

Fig. 1. PET CT of uterine PEComa illustrating a large centrally necrotic uterine mass with abnormal FDG (maximum SUV 7.1) uptake about its periphery, concerning for malignancy.

with physical exams every 3 months for 2–3 years with every 6–12 months imaging. The patient underwent a PET/CT at the 3 month follow up appointment which was negative for disease. PET/CT was performed given NCCN guidelines for PET/CT if metastasis is suspected. Given low suspicion of metastasis after negative PET/CT, she will receive CT chest/abdomen/pelvis every 6 months moving forward pending symptoms.

2. Discussion

PEComas are rare tumors, with only approximately 100 gynecologic PEComa cases reported (Liu et al., 2019). A distinct clinical presentation for PEComa is a challenge. Clinically, uterine PEComa usually manifests as abnormal vaginal or peritoneal bleeding and lower abdominal pain with a palpable mass (less frequently rupture of the uterus can be a presenting symptom), however a similar presentation is seen for many benign and malignant uterine tumors. Radiologic appearance is extremely variable a lack of consistent texture, dimension, and local or distal diffusion in PEComas. Radiologic diagnosis is therefore difficult and usually no more revealing than identifying a mass of unknown pathology (as it was in this case). In most reported gynecologic PEComa cases, pathologic diagnosis has been found difficult prior to hysterectomy as distinguishing a PEComa from benign leimyoma and sarcoma preoperatively with such methods as endometrial biopsy can be challenging. The preoperative diagnosis in this case is not the norm for uterine PEComa (Musella et al., 2015).

Operative intervention through total hysterectomy with bilateral salpingo-oophorectomy, with the aim of negative margins, represents the mainstay treatment in gynecologic PEComas. A complete resection is of paramount importance to evaluate the tumor for histopathologic prognostic risk factors. This correlates with NCCN guidelines regarding uterine sarcoma. Pathology from this case's specimen and expected pathology in PEComa can be found in Fig. 2. Histologic features found on microscopic examination can help predict aggressive behavior. These features were described by the World Health Organization in 2002 and state that any combination of infiltrative growth, marked hypercellularity, nuclear enlargement, hyperchromasia, high mitotic activity, atypical mitotic figures, and coagulative necrosis should be regarded as having a more aggressive behavior in terms of recurrence and metastases. These criteria were further refined, most recently by Conlon et al., to include tumor size > 5 cm, infiltrative growth pattern, high nuclear grade and cellularity, necrosis, mitotic activity > 1/50 HPF, and vascular invasion. Possession of these characteristics portends subsequent aggressive clinical behavior and malignancy. A tumor

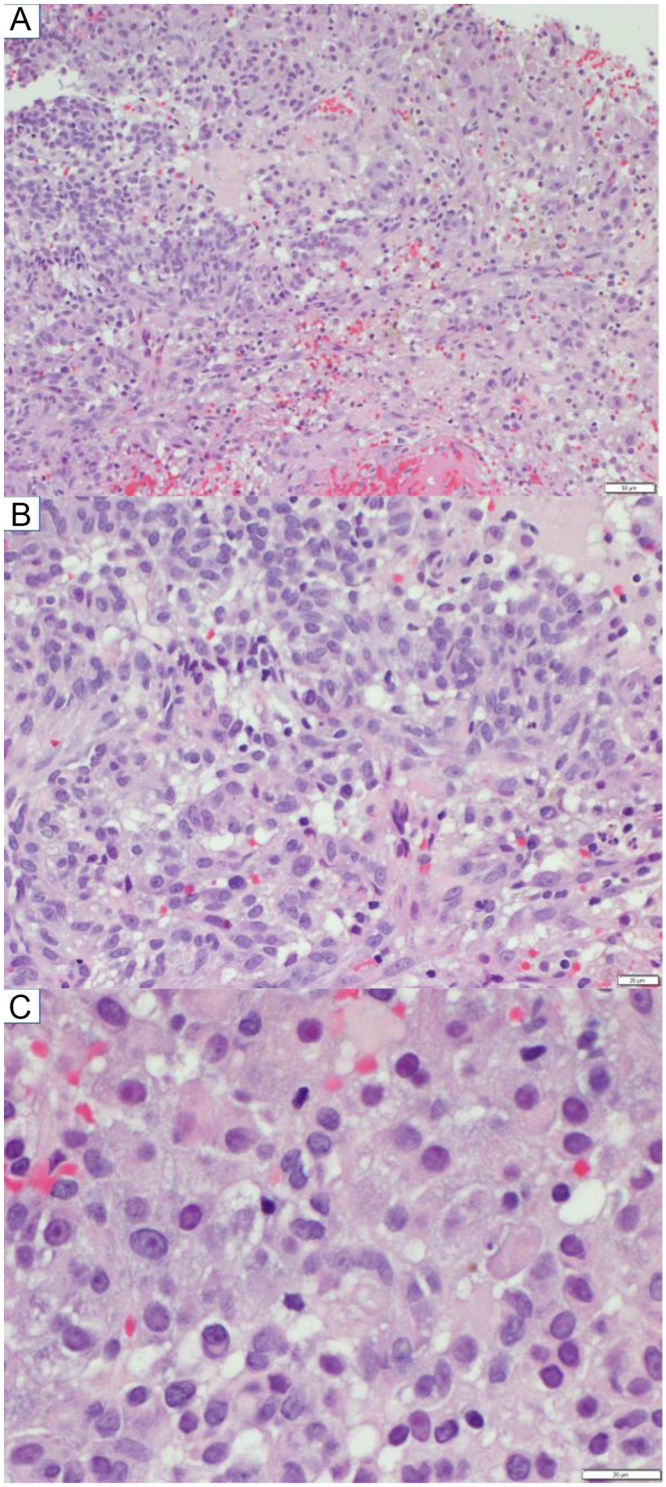

Fig. 2. A–C All H&E pathology slides: 100×, 200×, 400× respectively. The tumor consists of sheets and nests of cells with small to moderate sized nuclei with vesicular chromatin and distinct, occasionally prominent nucleoli. Cells have scant to moderate eosinophilic or clear cytoplasm, with occasional groups of cells with abundant granular eosinophilic cytoplasm. The tumor cells do not form glands, but are discohesive, and associated with islands of fibrous tissue. The periphery of the tumor shows cells with more epithelioid morphology. The tumor is generally well circumscribed; however, in some areas adjacent blood vessels show evidence of lymphovascular invasion. Patchy macroscopic areas of necrosis are seen. Immunostains support the diagnosis: HMB-45 and MART-1 (melanocytic markers): Positive (stains visible in Fig. 2C). MiTF (melanocytic): Patchy positive staining. Desmin and Smooth Muscle Actin (muscle markers): Patchy, weak to moderate positive staining (in cells with granular cytoplasm).

possessing none of these features suggested by Conlon et al. signifies a "benign" categorization. A tumor possessing only one the features: nuclear pleomorphism, multinucleated giant cell(s), or size > 5 cm gives a PEComa uncertain malignant potential. Finally, > 1 feature confers a "malignant" characterization to a PEComa, denoting likely aggressive behavior (Conlon et al., 2015). In our patient's uterine PEComa, 4 adverse prognostic features were detected; necrosis, size > 5 cm, an infiltrative edge, and lymphovascular invasion, favoring an increased risk of aggressive behavior. Given these prognostic factors favoring possible metastases, a delayed post-surgical PET CT was obtained and was found to be without disease.

Postoperatively, proper histologic identification is critical in gynecologic PEComa given the benefit which can be conferred with targeted therapy (Bennett et al., 2018). The role of targeted therapy comes about due to PEComas' common possession of mutations in tuberous sclerosis complex (TSC) genes *TSC1* and *TSC2*. These TSC gene products form a protein complex which negatively regulates mammalian target of rapamycin complex 1 (mTOR1), a crucial protein complex in cellular growth and protein synthesis. Mutation in these TSC genes therefore causes constitutive activation of this mTOR pathway and by extension unregulated, pathologic cellular growth (Dickson et al., 2013). mTOR inhibitors have, because of this mechanism, been described as a possible effective therapy in PEComa due to their actions on this pathologically active complex. Though evidence is sparse regarding this therapy's utility, several case reports and series display that mTOR inhibition can be well-tolerated with good radiologic responses, however, response is often short-lived and toxicity can be limiting (Benson et al., 2014). Though a lack of established guidelines exists, NCCN guidelines regarding uterine sarcoma and the above pathologic risk factor stratification and surveillance may be used. Regarding further treatment, while this aforementioned strategy of mTOR inhibitor use has been championed and does make some pathophysiologic sense, the therapeutic strategy in these tumors remains poorly established due to the rarity of their occurrence. Adjuvant chemotherapy and radiotherapy have proved disappointing in the treatment of malignant cases and are not suggested (Liu et al., 2016). The treatment of these tumors through attacking hormonal mechanisms may be a reasonable option. PEComas as a whole have an increased prevalence among female patients, in particular with regard to metastatic disease. Further, it has been hypothesized in lymphangioleiomyomatosis (LAM, a form of PEComa) that, in the presence of a TSC mutation, estrogen may inactivate the mitogen-activated kinase pathway causing increased neoplastic activity. Studies in TSC2-deficient mice with ER-positive LAM have shown an increase in cancer cellular survival, the number of cells present in circulation, and a 5 fold increase in pulmonary metastasis (Yu and Henske, 2010). In the vein of inhibiting these estrogen-mediated proliferative and survival mechanisms, the use of aromatase inhibitors in forms of PEComa, specifically LAM, have been described. However, such methods have never been described in uterine PEComa. Aromatase inhibitors bind to aromatase, an enzyme that catalyzes the conversion of androgen to estrogen, effectively depleting circulating levels of estrogen in the body (Le et al., 2014). The presenting symptom of DIC in this case is a unique presentation in PEComa. DIC has been reported in solid tumors in the past and is mediated in this setting by the generation of tissue factor (whether it be by tumor cells, endothelial cells, or the immune response). It has also been noted that tumor necrosis can trigger procoagulant pathways and trigger DIC. The principle of treatment in any patient with DIC is to try to eliminate the cause, meaning, in these patients with solid tumors, the tumor should be treated as soon as hemodynamic stability is regained. After treatment of and removal of coagulopathy, treatment with chemotherapy has been recommended in these cases of DIC, however, this is not possible in the above case of PEComa, as both chemotherapy and radiotherapy are generally ineffective (Feinstein, 2015). Coupling this with the idea that in an ER-positive PEComa survival and increased circulating cells have been seen, the use of letrozole was elected after complete resection of the tumor to control for both site-specific and potential circulatory and distant neoplasm which may be triggering DIC. It is encouraging and potentially supportive of the efficacy of this treatment that the patient remains without evidence of recurrent disease. Further, aromatase inhibitor use in this case is a reasonable choice because of their overall neutral effect on venous thromboembolism risk. This patient should not be at an increased risk of recurrent DVT due to Letrozole therapy.

The case report serves to further contribute to the scarce literature on uterine PEComas, including a relatively unique presentation, as well as a review of current proposed prognostic pathologic factors that may lead to increased risk of recurrence and metastases. Such cases may benefit for adjuvant therapy with mTOR inhibitors, or consideration for an aromatase inhibitor.

Author contributions

Rodger Rothenberger, MD and Caroline Billingsley, MD wrote the manuscript with support and input from Thomas Herzog, MD and Amanda Jackson, MD. Pathology images and commentary per Ady Kendler, MD, PhD.

Informed consent

Written informed consent was obtained from the patient 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.

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