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SMARCA4-deficient uterine sarcoma: A case report and a concise review

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ABSTRACT

Background: SMARCA4-deficient uterine sarcoma (SDUS) is a newly discovered undifferentiated uterine mesenchymal malignancy which has loss of expression of SMARCA4.
Case: A 46-year-old woman presented with heavy irregular vaginal bleeding over the previous 5 months. Computed tomography and magnetic resonance imaging showed a large pelvic mass centered within the uterus, suspicious of malignancy with regional metastatic lymphadenopathy. Biopsy confirmed SDUS and patient underwent chemotherapy. Her symptoms improved 3 months after treatment.
Conclusion: An extremely rare case of this newly described entity is reported. Recognizing the characteristic imaging and pathology findings of SDUS is essential for an accurate diagnosis, which may affect patient survival.

1. Introduction

SMARCA4-deficient uterine sarcoma (SDUS) is an extremely rare but very aggressive tumor which has loss of expression of SMARCA4 (BRG1) [1]. It is a subset of undifferentiated uterine sarcomas with rhabdoid and small cell features [1,2], and shares similar mutations with small cell carcinoma of the ovary (hypercalcemic type), although it is considered a different entity [3]. To our knowledge, there are fewer than 20 published cases of SDUS. In this study, we present a rare case of SDUS and a concise review of the imaging and clinicopathologic presentation of patients with SDUS.

2. Case Report

A 46-year-old woman, G0P0, presented to the emergency department with chronic vaginal bleeding that had started 5 months previously and acute heavy vaginal bleeding over the past 2 days. The patient complained of lightheadedness, fatigue, shortness of breath, difficulty voiding and defecating, lower-extremity swelling and 20-pound weight loss over the past month. The medical history was positive for uterine leiomyomas with enlarged uterus and longstanding amenorrhea. The patient had had irregular menstrual cycles every 3 to 6 months for the past several years, and denied any menstrual period during the past year. Physical exam was remarkable for a firm, irregularly shaped mass above the umbilicus and non-pitting edema in the lower extremities bilaterally. A pelvic exam revealed normal external genitalia with a large cervical mass for which she underwent biopsy under anesthesia.

Computed tomography (CT) of the chest, abdomen and pelvis demonstrated an enlarged lobular uterus with a large midline pelvic mass, retroperitoneal and pelvic lymphadenopathy, and mild bilateral hydronephrosis, likely due to distal ureteral obstruction (Fig. 1). Magnetic resonance imaging (MRI) of the pelvis with contrast confirmed the large uterine mass involving nearly the entire cervix and uterus with multiple likely metastatic pelvic and retroperitoneal lymph nodes (Fig. 2). The pathology study from the biopsy (Fig. 3) showed sheet-like solid growth of undifferentiated epithelioid cells with round, ovoid nuclei, minimal pleomorphism, and prominent nucleoli. Extensive necrosis was present. Immunohistochemical stains revealed loss of SMARCA4 (BRG1), SMARCA2 (BRM), claudin-4, and E-cadherin with retained SMARCB1 (INI1). INSM1 and CK18 were negative. These findings were most compatible with a diagnosis of SDUS.

Doppler ultrasound to investigate the lower-extremity swelling was positive for an acute thrombus in the left common femoral vein. The patient was started on anticoagulation, but it was stopped due to continued vaginal bleeding requiring multiple transfusions; therefore, an IVC filter was placed. The bilateral hydronephrosis was further assessed with a nuclear medicine renal scan which demonstrated decreased left kidney function, and therefore an anterograde left ureteral stent was placed. The patient was started on chemotherapy with Gemcitabine 675 mg/m2 IVPB, Docetaxel 75 mg/m2 IVPB, and Neulasta 6 mg SC per American Cancer Society guideline [4], and regularly followed up as an outpatient. At the last follow-up visit, 3 months after starting the chemotherapy, the patient reported improved vaginal bleeding, and

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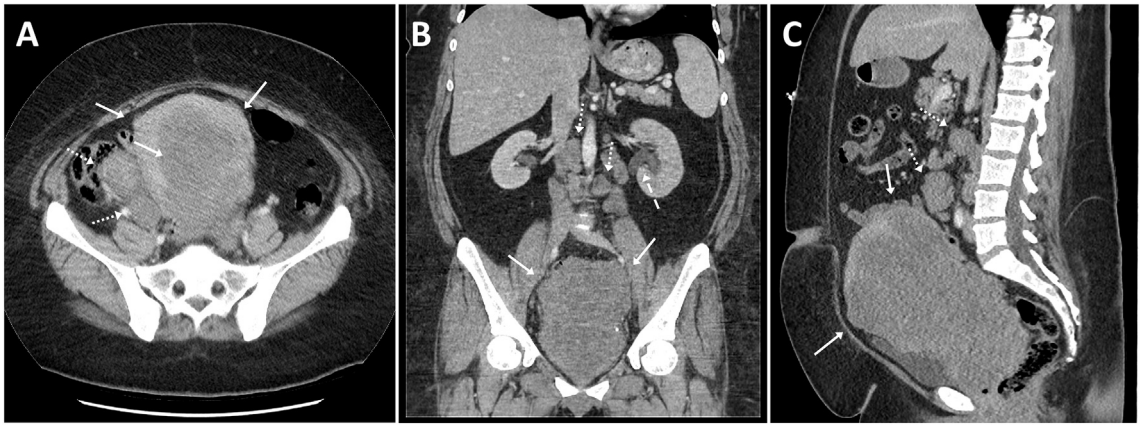

Fig. 1. Axial (A), coronal (B), and sagittal (C), contrast-enhanced CT shows a very large heterogeneous uterine mass replacing the endometrium and cervix (solid arrows A, B, C) and multiple enlarged regional and retroperitoneal lymph nodes (dotted arrows, A, B, C). Mild left hydronephrosis is partially visualized (dashed arrow, B) secondary to external compression on the distal left ureter from the uterine mass.

denied lightheadedness, shortness of breath, difficulty voiding and defecating.

3. Discussion

Uterine sarcoma is a rare type of uterine cancer that is estimated to range between 3% and 5% of all neoplasms of the uterine corpus [5,6]. The incidence of uterine sarcomas ranges from 1.55 to 1.95 per 100,000 females per year [6]. Uterine sarcomas are classified into two different groups, mesenchymal tumors and mixed epithelial and mesenchymal tumors [5,6]. SDUS is a newly discovered undifferentiated uterine mesenchymal malignancy with unique clinicopathologic features [1,5]. Patients with SDUS usually present with vaginal bleeding, and with cervical or uterine masses on physical examination and imaging [2,7]. It mostly affects young women; the mean patient age is 36 years, which is much younger than patients with undifferentiated endometrial carcinomas (mean age 61 years) [7], but slightly older than patients with small cell carcinoma of the ovary, hypercalcemic type (mean age 29 years) [3].

The clinical manifestations of SDUS are non-specific and imaging is usually required for diagnosis. Nevertheless, the imaging characteristics of SDUS are not well described, but likely share similar findings to other undifferentiated uterine sarcomas. MRI should be performed to assess the local invasion of the lesion. The T2-weighted MRI sequence is considered superior to CT and ultrasonography for detecting myometrial invasion [8,9]. MRI may show a heterogeneous signal-intensity endometrial mass with low-intensity bands scattered in the areas of myometrial involvement, intramyometrial worm-like nodular extensions, indicating myometrial and lymphovascular invasion of the tumor [3,8,10,11]. There may be associated high Intensity on diffusion-weighted imaging (DWI) with low apparent diffusion coefficient (ADC) values [10]. CT is mainly required for disease staging for distal metastasis rather than diagnosis and usually shows a large heterogeneous mass with multifocal areas of deep myometrial invasion [3,10,11].

Diagnosis of SDUS is usually based on morphology and loss of SMARCA4 staining via the anti-SMARCA4 antibody [2]. SDUS is microsatellite stable and lacks significant expression of epithelial markers like claudin-4 [1,2,7]. On histology, SDUS typically shows diffuse sheets of medium to large epithelioid cells with areas of rhabdoid morphology, corded architecture with stromal hyalinization, and focal phyllodiform architecture [2,7]. The histology of the cervical biopsy in our patient showed sheet-like solid growth of undifferentiated epithelioid cells with round, ovoid nuclei, minimal pleomorphism, prominent nucleoli with extensive necrosis. Immunohistochemical stains showed loss of SMARCA4 (BRG1), SMARCA2 (BRM), claudin-4, and E-cadherin with retained SMARCB1 (INI1), most compatible with SDUS.

The main differential diagnoses of SDUS are undifferentiated endometrial carcinomas, small cell carcinoma of the ovary (hypercalcemic type), and adenosarcoma. Compared with undifferentiated endometrial carcinomas, SDUS more frequently shows phyllodiform architecture, and less frequently expresses TP53 mutations, microsatellite instability, and is characterized only by inactivating mutations in SMARCA4 [7]. SDUS and small cell carcinoma of the ovary (hypercalcemic type) both affect young women, are fatal with aggressive clinical behavior and share inactivation of SMARCA4 [3]. Patient with SDUS present with cervical or uterine mass and vaginal bleeding, and are negative for WT-1 [12], whereas small cell carcinoma of the ovary (hypercalcemic type) presents as an ovarian mass with abdominal pain [2]. It may be histologically difficult to differentiate uterine metastasis of the large cell variant of small cell carcinoma of the ovary (hypercalcemic type) from SDUS [2,13]. The focal phyllodiform growth seen in SDUS is a feature that can be present in adenosarcoma of the uterus and cervix, although inactivation of SMARCA4 has not be seen in adenosarcoma and is seen only in SDUS [14]. This growth pattern is not specific to adenosarcoma and can be seen in other tumors, including carcinosarcoma and benign endometrial polyps [15]. Carcinosarcomas may have a low-power resemblance to adenosarcomas, which is usually a focal finding and without any stromal condensation [16]. Diffuse epithelioid morphology, lack of periglandular stromal condensation and high-grade atypia in this component favor SDUS compared to adenosarcomas [2].

Other differential diagnoses include grade-3 endometrioid carcinoma, high-grade endometrial stromal sarcoma, epithelioid leiomyosarcoma, malignant PEComa, lymphoma [7], and malignant peripheral nerve sheath tumor [17]. SDUS lacks significant epithelial marker expression, including keratin, epithelial membrane antigen (EMA), cytokeratin 7 (CK7) and claudin-4, which differentiates it from endometrioid carcinomas [2,18]. Endometrial stromal tumors show strong staining of CD10 and the high-grade component stains for Cyclin D1, which are not findings in SDUS [19]. Smooth muscle uterine tumors like leiomyosarcomas express SMA, desmin, muscle-specific actin (MSA), and caldesmon [20]. Epithelioid leiomyosarcoma and malignant PEComa are positive for smooth muscle markers and show complex chromosomal abnormalities [21,22]. In addition, PEComas are immunoreactive to HMB-45 [22]. SDUS, in contrast, is negative for smooth muscle markers and HMB-45 and does not have complex chromosomal abnormalities [1,2]. Lymphoma can be seen as primary or secondary in the uterus [23]. CD45 as a leucocyte common antigen is a specific marker for lymphoma and may be helpful in differentiating it from SDUS [23]. Malignant peripheral nerve sheath tumors are aggressive

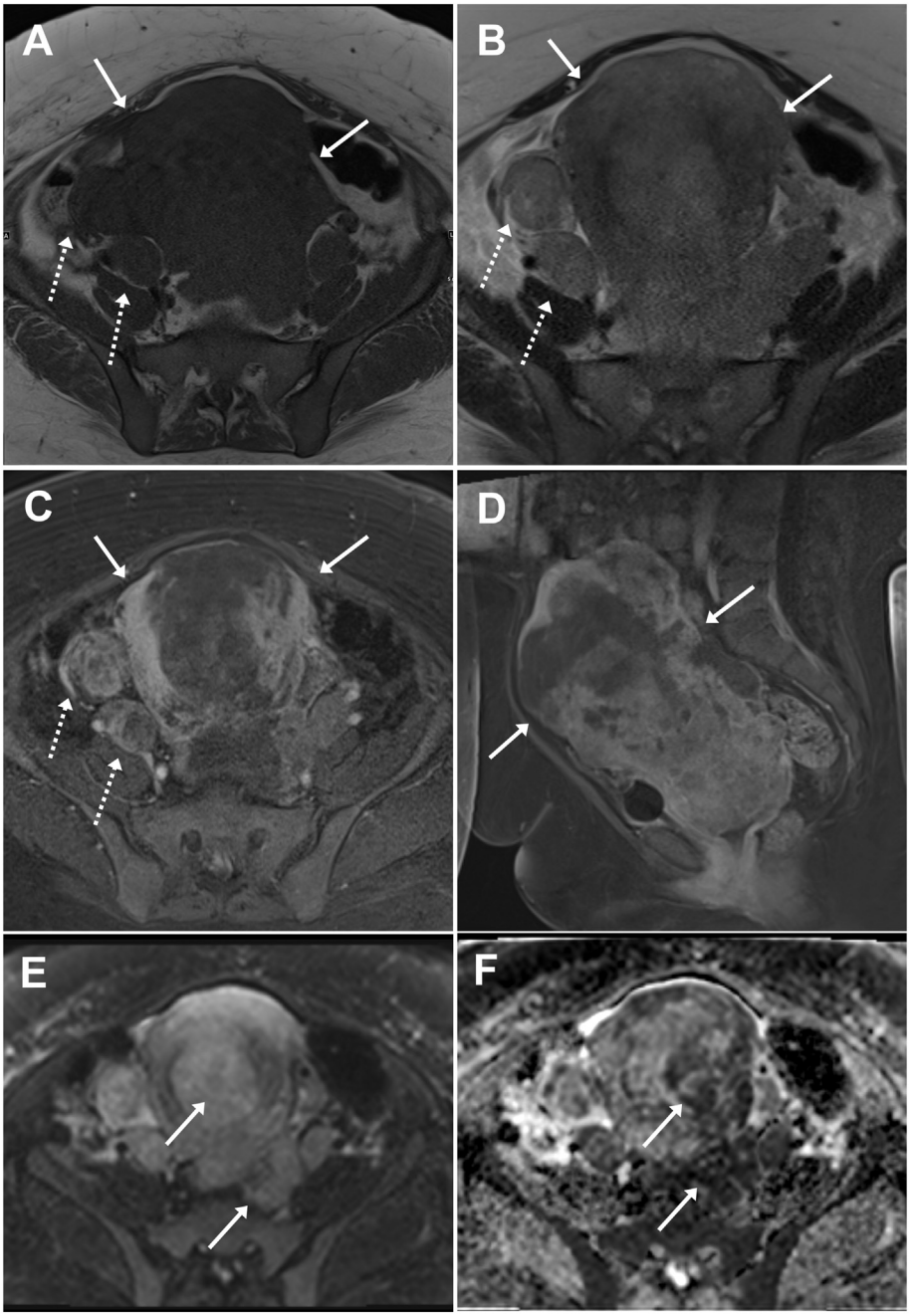

Fig. 2. Axial noncontrast T1-weighted (A), T2-weighted (B), and postcontrast axial (C) and sagittal (D) fat-saturated T-1 weighted MR images demonstrate a large heterogeneous mass centered within the uterus and cervix (solid arrows, A–D) and regional enlarged lymph nodes (dotted arrows, A–D). The mass is hypointense on T-1 weighted images with mixed signal intensity on T-2 weighted images and heterogeneous enhancement. There are areas with increased signal intensity on DWI (solid arrows, E) and decreased signal intensity on ADC maps (solid arrows, F) within the mass.

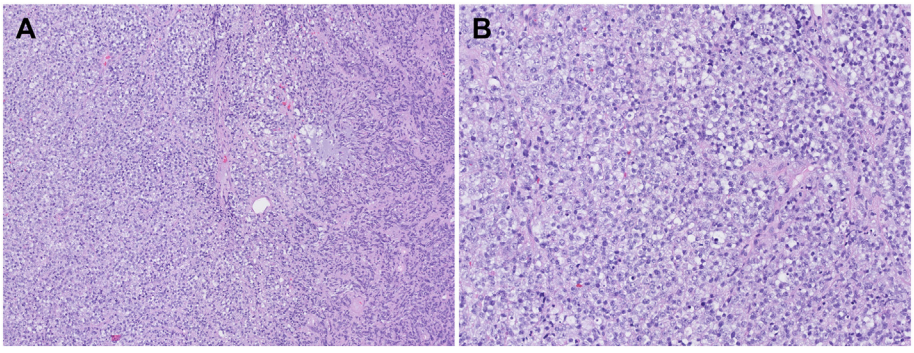

Fig. 3. Low-power 5X: 50X magnification (A) showing diffuse effacement of normal cervix by malignant cells. High-power 20X: 200X magnification (B) showing diffuse pleomorphic malignant cells.

soft-tissue tumors and may rarely involve the uterus and are positive for S100, which is not seen in SDUS [17].

It may be clinically important to histologically identify SDUS because of its aggressive behavior, but also because of emerging targeted therapies [1] and their effects on patients' survival. Most patients with SDUS show lymphovascular invasion and extrauterine spread and metastasis at the time of presentation [2]. Total abdominal hysterectomy with or without bilateral salpingo-oophorectomy is the surgical standard of care for uterine sarcomas [3,11,24]. Preservation of the ovaries can be considered in premenopausal patients and should be individualized based on the clinical scenarios and intraoperative findings [11,25]. The median survival despite aggressive treatment with surgery is 9 months, which is shorter than for undifferentiated endometrial carcinomas (36 months) [7]. New medical therapies, including D-L1, EZH2 anti-PD-1, and CDK4/6 inhibitors, have shown promising results in similar malignancies like small cell carcinoma of the ovary, hypercalcemic type [2,3,7,24]. Further studies are warranted to assess the effectiveness of these new medical treatments on patients with SDUS.

4. Conclusion

In summary, an extremely rare case of this newly described entity is reported. Recognizing the characteristic imaging and pathologic findings of SDUS is essential for an accurate diagnosis, which may affect patient's survival.

Contributors

Ali Kord designed the study, helped with drafting the manuscript, data collection and online search, and with data analysis, image analysis and interpretation.

Atul Eppurath helped with drafting the manuscript, data collection and online search.

Hamidou Drammeh helped with drafting the manuscript, data collection and online search.

Ismail Elbaz Younes helped with drafting the manuscript, data collection and online search, and with data analysis, image analysis and interpretation.

Karen L. Xie designed the study, helped with drafting the manuscript, data collection and online search, and with data analysis, image analysis and interpretation.

All authors helped with revision and approved the final draft.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

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