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SMARCA4-Deficient Undifferentiated Uterine Sarcoma Presenting as Nonpuerperal Uterine Inversion in a Morbidly Obese Woman: A Case Report

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Abstract

SMARCA4-deficient undifferentiated uterine sarcoma (SDUS), which mainly occurs in young patients, is a recently recognized, highly aggressive malignancy with an extremely poor prognosis. Nonpuerperal uterine inversion (NPUI) is a rare condition most commonly associated with uterine tumors. Here, we report a case of NPUI caused by SDUS. A 25-year-old woman (body mass index, 48 kg/m²) presented with irregular vaginal bleeding. Pelvic examination revealed a vaginal mass extending from the cervix to the introitus region. Pelvic magnetic resonance imaging revealed uterine inversion secondary to an endometrial mass. Tumor scrape cytology showed no malignant cells. Tumor resection and uterine repositioning were performed to preserve fertility. Histopathological examination findings revealed an undifferentiated malignant tumor, while immunohistochemical analysis confirmed a diagnosis of SDUS. Computed tomography revealed para-aortic lymph node enlargement, suggesting metastatic involvement. The patient subsequently underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and excision of an enlarged para-aortic lymph node. Based on these pathological findings, the patient was diagnosed with SDUS with para-aortic lymph node metastasis (FIGO stage IIIC) and received adjuvant chemotherapy with doxorubicin. Following completion of six chemotherapy cycles, our patient remained disease-free at 12 months postoperatively. This is the first reported case of SDUS presenting as NPUI in a patient with severe obesity. Optimal management of SDUS has not yet been established, but complete surgical resection may play an important role in disease control.

Categories: Obstetrics/Gynecology, Pathology, Oncology
Keywords: fertility preservation, nonpuerperal uterine inversion, obesity, smarca4-deficient undifferentiated uterine sarcoma, uterine sarcoma

Introduction

SMARCA4-deficient uterine sarcoma (SDUS) is a rare and highly aggressive subtype of undifferentiated uterine sarcoma, characterized by the loss of SMARCA4 (BRG1), a key component of the SWI/SNF chromatin remodeling complex [1]. A limited number of such cases have been reported worldwide, and comprehensive clinical data are available for only a small subset. The largest case series to date, reported by Wang et al. [2], comprised 18 cases, demonstrating that this malignancy predominantly affects young women and is associated with poor clinical outcomes. Histologically, SDUS commonly demonstrates undifferentiated and rhabdoid features, making diagnosis challenging [3], and is characterized by immunohistochemical confirmation of SMARCA4 loss. Because of its rarity, optimal treatment strategies have not yet been established.

Nonpuerperal uterine inversion (NPUI) is a rare condition in which the uterine fundus collapses inward unrelated to childbirth. NPUI is most commonly associated with benign tumors, such as submucosal leiomyomas, whereas malignant causes are less common [4]. Patients typically present with vaginal bleeding, pelvic pain, and a vaginal mass, with imaging modalities, such as magnetic resonance imaging (MRI), essential for diagnosis.

We report a patient with NPUI caused by a uterine tumor for whom fertility-preserving surgery was initially performed, followed by a diagnosis of SDUS and subsequent definitive surgery.

Case Presentation

A 25-year-old nulligravida with a body mass index of 48 kg/m² presented with irregular vaginal bleeding and severe anemia. Contrast-enhanced magnetic resonance imaging (MRI) performed at a referring institution revealed findings suggestive of uterine inversion, with the inverted uterus extending into the

distended vaginal cavity. A heterogeneously enhancing mass measuring 40 mm in diameter was identified at the distal end of the inverted uterus. However, the imaging findings could not reliably distinguish between benign and malignant tumors. Myometrial invasion could not be reliably assessed because of the distorted uterine anatomy (Figure *1*). Tumor scrape cytology was negative for malignant cells. The patient was subsequently referred to our hospital for further evaluation and management. The patient was hemodynamically stable on admission. Vaginal examination revealed a foul-smelling brownish discharge and a tumor in the vagina. Uterine repositioning was attempted on hospital day 3 after admission.



FIGURE 1: Pelvic MRI of the uterine inversion

(A) Sagittal T2-weighted image showing inversion of the uterine fundus and an associated tumor extending toward the vagina.

(B) Contrast-enhanced sagittal image demonstrating the inverted uterus and associated tumor.

(C) Axial T2-weighted image showing the concentric configuration of the inverted uterine structures.

Arrows indicate the tumor.

MRI, magnetic resonance imaging

Because a definitive diagnosis of malignancy could not be established preoperatively, fertility-preserving surgery was initially performed to obtain a histopathological diagnosis and control vaginal bleeding.

We first performed surgical vaginal tumor debulking to reduce the tumor volume, followed by manual uterine repositioning using the Johnson procedure, which was unsuccessful. We then proceeded with a laparoscopic approach and attempted upward traction of the round ligaments and uterine fundus (Huntington's procedure), but repositioning remained unsuccessful. Subsequently, an incision was made on the posterior aspect of the cervical constriction ring (the Haultain procedure) to facilitate reduction. However, laparoscopic reduction could not be achieved, necessitating conversion to laparotomy. Following additional tumor debulking, the uterine inversion was successfully reduced manually (Figure *2*).

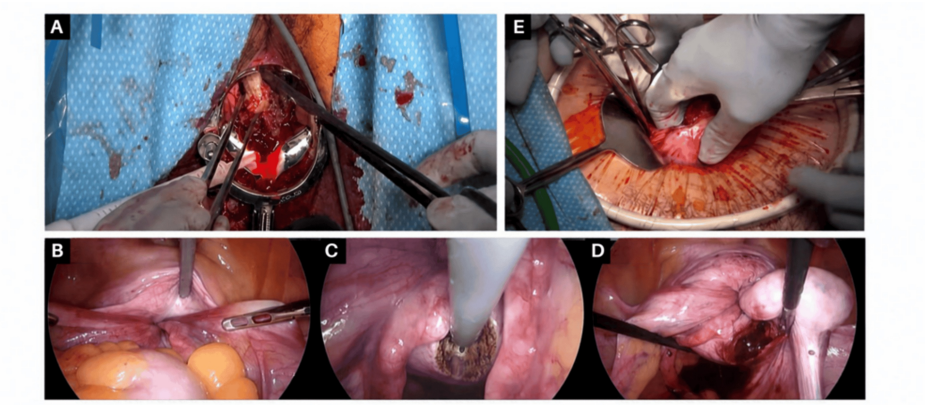


FIGURE 2: Surgical procedures for uterine repositioning

(A) Vaginal tumor debulking was performed to reduce the tumor volume, followed by an attempt at manual uterine repositioning using the Johnson procedure.

(B) The round ligaments were grasped with forceps and gently pulled cranially (Huntington procedure).

(C) A longitudinal incision was made in the posterior uterine wall (Haultain procedure).

(D) Despite attempts using the Johnson, Huntington, and Haultain procedures, uterine repositioning remained unsuccessful.

(E) The procedure was converted to laparotomy, with uterine inversion successfully corrected.

Histopathological examination of the resected tumor revealed an undifferentiated malignant tumor of uterine origin, although definitive histological classification was challenging. The tumor consisted of solid sheets of undifferentiated cells with a high nuclear-to-cytoplasmic ratio, vesicular nuclei, and prominent nucleoli. Mild to moderate nuclear size variation was observed without marked nuclear pleomorphism. Focal rhabdoid morphology, focal necrosis, and mitotic figures were also present. Atrophic, non-neoplastic endometrial glands were entrapped within the tumor. Immunohistochemical analysis demonstrated that the tumor cells were focally positive for PAX8 and progesterone receptor, and negative for estrogen receptor, desmin, α-smooth muscle actin, p53, cyclin D1, CD3, CD10, CD20, AE1/AE3, Ber-EP4, EMA and WT-1 (clones 6F-H2 and C-19). Additional immunohistochemical staining revealed loss of SMARCA4 expression, confirming SMARCA4 deficiency (Figure 3). Comprehensive genomic profiling (GenMineTOP®, GenMine Labs Corp, Tokyo, Japan) identified a SMARCA4 gene mutation (c.299C>A), and the tumor mutational burden was low (2.1 muts/Mb).

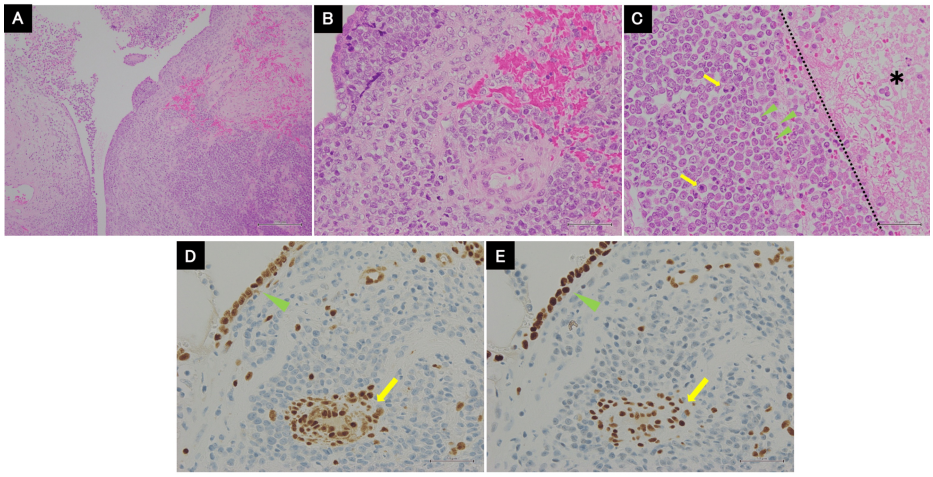


FIGURE 3: Histopathological and immunohistochemical findings

(A, B) Hematoxylin and eosin (H&E) staining showing solid sheets of undifferentiated tumor cells with a high nuclear-to-cytoplasmic ratio, vesicular nuclei, and prominent nucleoli (A, ×10; B, ×40).

(C) H&E staining showing mitotic figures (arrows), rhabdoid tumor cells (arrowheads), and focal necrosis (asterisk) (×40).

(D, E) Immunohistochemical staining showing loss of SMARCA2 (D) and SMARCA4 (E) expression in tumor cells, with retained expression in vascular structures(arrow) and non-neoplastic endometrial glands(arrowhead) (×40).

H&E, hematoxylin and eosin

Postoperative contrast-enhanced MRI and positron emission tomography-computed tomography revealed no residual uterine lesions; however, para-aortic lymph nodes suggestive of metastasis were detected (Figure 4). Given the tumor's poor prognosis and suspected lymph node metastasis, fertility preservation was deemed unfeasible, and definitive surgical treatment was undertaken. Owing to the patient's severe obesity, total hysterectomy with bilateral salpingo-oophorectomy and excision of an enlarged para-aortic lymph node was performed for tumor debulking using an open approach.

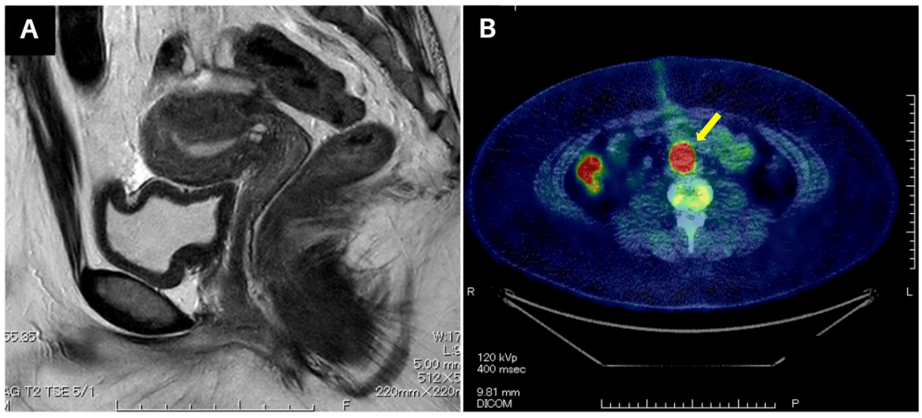


FIGURE 4: MRI after initial surgery

(A) MRI showing no evidence of residual tumor in the uterus.

(B) Positron emission tomography-computed tomography (PET-CT) image showing increased tracer uptake in a para-aortic lymph node, suggestive of metastasis (arrow).

MRI, magnetic resonance imaging

Histopathological examination findings revealed a tumor measuring 30 × 20 × 20 mm with myometrial invasion and positive lymphovascular space invasion. Para-aortic lymph node metastasis was also confirmed. Based on these findings, the final diagnosis was SMARCA4-deficient undifferentiated uterine

sarcoma (SDUS). As no specific staging system has been established for SDUS, the tumor was classified as FIGO 2009 stage IIIC and pT1aN1M0 according to the staging systems for uterine leiomyosarcoma and endometrial stromal sarcoma (UICC 8th edition for TNM classification) [5,6].

The patient received adjuvant chemotherapy with doxorubicin; after completion of 6 cycles, the patient remained disease-free at 12 months of follow-up.

Discussion

SDUS is a recently recognized clinicopathological entity characterized by aggressive behavior and poor clinical outcomes. Since first reported by Kolin et al. in 2018 [7], the number of reported SDUS cases has gradually increased; however, many aspects of its pathogenesis, optimal management, and prognosis remain unclear. This case report describes a challenging clinical scenario involving a patient with severe obesity, NPUI, and SDUS, which is a rare and complex combination of conditions.

Uterine inversion is classified into puerperal (obstetric) and nonpuerperal (gynecological) types [8]. Puerperal uterine inversion occurs in approximately 1 in 2,000-20,000 deliveries and is usually associated with childbirth or miscarriage, whereas NPUI is extremely rare, with an unknown incidence [9]. The mean age at presentation is reported to be 46.3 years, making its occurrence in women in their 20s uncommon. NPUI is multifactorial and involves increased tumor weight, traction, and intra-abdominal pressure. In cases of sarcoma, tumor growth may weaken the uterine wall, facilitating prolapse and inversion [10]. Leiomyomas are the most common cause (57.2%), followed by sarcomas (13.5%). Most patients (86.8%) are treated with hysterectomy predominantly via an abdominal approach [4]. The aggressive growth of SDUS may have contributed to uterine inversion in the present case, although the precise mechanism remains uncertain. Preoperative MRI could not reliably distinguish between benign and malignant tumors or assess myometrial invasion, and tumor scrape cytology was negative for malignant cells. The negative cytology result may have been attributable to sampling error, as active tumor bleeding may have limited adequate sampling during the scraping procedure. Uterine inversion can distort normal uterine anatomy, complicating radiologic assessment of tumor origin and myometrial invasion. Given the patient's young age (25 years), nulligravid status, and the absence of a definitive preoperative diagnosis of malignancy, we initially adopted a uterus-preserving surgical approach involving tumor resection and reduction of the uterine inversion.

SDUS predominantly affects young women (median age, 34 years) and is associated with an extremely poor prognosis (median survival, approximately 9 months) [2]. Most patients present with abnormal vaginal bleeding and a uterine, cervical, or vaginal mass, with approximately 50% having lymph node or distant metastases at the time of diagnosis. The differential diagnosis of SDUS includes undifferentiated endometrial carcinoma (UDEC), grade 3 endometrioid carcinoma, carcinosarcoma, adenosarcoma, and high-grade endometrial stromal sarcoma (HG-ESS). Although UDEC shares morphological features with SDUS, UDEC and grade 3 endometrioid carcinoma were considered less likely in the present case because of the absence of epithelial marker expression. UDEC may also exhibit greater nuclear pleomorphism, TP53 mutations, or microsatellite instability [3]. Carcinosarcoma was not favored because the entrapped endometrial glands lacked cytologic atypia and the tumor cells were negative for epithelial markers. Adenosarcoma was considered unlikely because periglandular stromal cuffing was absent, whereas HG-ESS was less favored because characteristic stromal growth patterns and myxoid or hyalinized changes were not observed. The combined morphological and immunohistochemical findings, particularly the loss of SMARCA4 and SMARCA2 expression, together with the identification of a SMARCA4 gene mutation by comprehensive genomic profiling, supported the diagnosis of SDUS. Accurate differentiation requires comprehensive histopathological, immunohistochemical, and molecular evaluation because of its prognostic and therapeutic implications.

Regarding treatment, the optimal management of SDUS has not yet been established because of the limited available evidence. Complete surgical resection, typically involving total hysterectomy with bilateral salpingo-oophorectomy, is considered the mainstay treatment and essential for disease control. The role of lymphadenectomy remains unclear; however, it may be useful for accurate staging as lymph node metastasis has been reported in several cases [11]. The 2026 National Comprehensive Cancer Network (NCCN) guidelines list doxorubicin monotherapy as a preferred first-line systemic treatment option for advanced, recurrent, or unresectable uterine sarcoma [12]. In addition, a previous literature review reported the use of doxorubicin-based chemotherapy in several patients with SDUS [2]. However, the efficacy of adjuvant chemotherapy specifically for SDUS remains uncertain. In the present case, given the aggressive nature of SDUS and the presence of histologically confirmed para-aortic lymph node metastasis, adjuvant chemotherapy with single-agent doxorubicin was selected with reference to the NCCN guidelines and previously reported cases. The role of radiotherapy in SDUS remains unclear because of the limited available evidence, particularly in the adjuvant setting. Postoperative radiotherapy was not considered in the present case. Immunotherapy research is growing. SMARCA4 function allows transcription of key immune-related genes. SMARCA4 loss leads to transcriptional repression, silences immune pathways, and increases Enhancer of Zeste Homolog 2 (EZH2) expression that promotes an immunosuppressive phenotype [13]. Emerging therapies, including immune checkpoint inhibitors and targeted agents, such as EZH2 inhibitors, have shown potential therapeutic benefits [2]. Further studies are required to establish optimal treatment strategies.

Following the diagnosis of SDUS and the detection of para-aortic lymph node enlargement, definitive surgery was performed, followed by six cycles of adjuvant doxorubicin. The patient remained disease-free at 12 months postoperatively. Although this outcome is encouraging, the relatively short follow-up period and the single-case nature of this report preclude conclusions regarding the efficacy of adjuvant doxorubicin or long-term disease control. Continued surveillance and further accumulation of clinical evidence are necessary.

Conclusions

We report a rare case of NPUI caused by SDUS in a young woman with severe obesity. This case highlights the diagnostic challenges of SDUS, as preoperative cytology was negative for malignancy despite the presence of an aggressive uterine tumor. Although fertility-preserving surgery was initially performed because of the patient's young age and the absence of a preoperative diagnosis of malignancy, definitive surgery was subsequently performed following the diagnosis of SDUS. This case emphasizes that underlying malignancy should be considered in patients presenting with NPUI, even at a young age. Although complete surgical resection was achieved and the patient remained disease-free at 12 months postoperatively, the limited follow-up period precludes conclusions regarding long-term disease control.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Saori Takeuchi, Eiji Kondo

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Clinical Research Ethics Review Committee of Mie University Hospital issued approval H2019-164. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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