SMARCA4-deficient uterine adnexal tumor with ascites: A case report and literature review

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Abstract. SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4 (SMARCA4)-deficient tumors are rare and highly aggressive tumors characterized by a loss of SMARCA4 expression, and SMARCA4-deficient tumors in the adnexal area of the uterus are particularly rare. The present study describes the case of a 64-year-old woman who was admitted to Weifang People's Hospital (Weifang, China) with abdominal distension, and was observed to have a mass with ascites in the adnexal area of the uterus. Based on clinical, imaging and pathological findings, the patient was diagnosed with a SMARCA4-deficient adnexal tumor with ascites. Biopsy of the left and right adnexal lesions was performed, and the patient was administered chemotherapy. After one cycle of bevacizumab, sindilizumab and carboplatin, no further treatment was administered. After biopsy and chemotherapy, the abdominal distension was alleviated and the general condition of the patient was satisfactory. The patient was followed up and died 3 months after treatment. Notably, it is important to avoid misdiagnosing this tumor as other types of adnexal uterine tumors, and morphological and immunohistochemical features may be useful for diagnosing primary SMARCA4-deficient tumors in the adnexal area of the uterus.

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Abbreviations: SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4; NGS, next-generation sequencing; PAX-8, paired box gene 8; CK, cytokeratin; Syn, synaptophysin; TTF-1, thyroid transcription factor-1; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; MyoD1, myogenic differentiation 1; WT-1, Wilms tumor gene; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PMS2, postmeiotic segregation increased 2; SCCOHT, small cell carcinoma of the ovary hypercalcemic type

Key words: SMARCA4-deficient tumor, adnexal area, chemotherapy, misdiagnosis, morphological and immunohistochemical features

Introduction

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4 (SMARCA4)-deficient tumors are prone to misdiagnosis because of their lack of specific differentiation, and are associated with a rapid progression and poor prognosis (1). Previous reports of SMARCA4-deficient tumors mainly refer to individual cases in multiple organs and sites, such as the nasal cavity and sinuses (2), chest and lung (3), gastrointestinal tract (4,5) and uterus (6). The main types of SMARCA4-deficient tumors in the uterus are: Undifferentiated and dedifferentiated endometrial cancer, and SMARCA4-deficient undifferentiated uterine tumors. The former accounts for 1-2% of endometrial cancer cases, mostly occurs during the perimenopause and the prognosis is poor; notably, the prognosis of undifferentiated endometrial cancer is worse in SMARCA4-deficient cases. SMARCA4-deficient undifferentiated uterine tumors tends to occur in young people and have a worse prognosis than undifferentiated and dedifferentiated endometrial cancer. At present, the absence of SMARCA4 in poorly differentiated uterine malignancies can be detected by immunohistochemistry, which helps to identify SMARCA4-deficient tumors and make a differential diagnosis with other malignancies. SMARCA4-deficient tumors are highly aggressive tumors that do not respond well to conventional treatment (3-5). The present study describes the case of a SMARCA4-deficient tumor in the adnexal region of the uterus with ascites. The present case report may improve the understanding of this novel group of diseases.

Case report

Ethic approval. The present study was approved by the Institutional Review Board of Weifang People's Hospital (First Affiliated Hospital of Shandong Second Medical University) (Weifang, China; approval no. KYLL20240105-2). Written informed consent was obtained from the patient for the

publication of this case report and the accompanying images. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical history. A 64-year-old woman presented at Weifang People's Hospital (Weifang, China) in May 2023 with abdominal distension and increased stool frequency for >10 days. Computed tomography evaluation showed dense soft tissue in the left adnexal area, with the interior showing a spot-like high density; the tumor was ~6.6x4.1 cm in size (Fig. 1). No abnormalities were observed in the liver, gallbladder, pancreas, bladder, bilateral kidneys or adrenal glands. The uterus was normal in size and shape. The retroperitoneal and omental adipose spaces were blurred; nodules were observed, and there were large amounts of fluid in the abdominal and pelvic cavities. The blood calcium concentration was slightly lower than normal at 1.95 mmol/l (normal range, 2.11-2.58 mmol/l), tumor marker CA125 level (32.30 U/ml) was slightly higher than normal (0-16 U/ml), and tumor marker CA199 14.47 U/ml (normal range, 0-34 U/ml) and carcinoembryonic antigen (CEA) 1.04 ng/ml (0-5 ng/ml) levels were normal. After preoperative examination, laparoscopic exploration was performed; during the operation, a large number of bleeding ascites in the pelvic cavity and abdominal cavity was observed, the surface of the uterus was covered with crumbly-textured lesions, the left fallopian tube and ovary were wrapped together with a diameter of ~10 cm, the right ovary was atrophied with small lesions on the surface and the right fallopian tube appeared normal. Because extensive lesions were observed, the left and right adnexal lesions were biopsied (Fig. 2A). The pelvic effusion disappeared after four cycles of peritoneal thermoperfusion chemotherapy with 30 mg cisplatin (Fig. 3A and B). Bevacizumab injection (500 mg on day 0), docetaxel (90 mg on day 1) and carboplatin (400 mg on day 2) was administered for three cycles, after which the disease was advanced (Fig. 3C and D). After one cycle of bevacizumab (500 mg on day 0), sindilizumab (500 mg on day 0) and carboplatin (500 mg on day 1), no further treatment was administered. The patient died of multiple organ metastasis 9 months after the start of treatment.

Immunohistochemical staining and gene sequencing. The biopsied specimens were fixed in 10% neutral-buffered formalin for 24 h at room temperature, embedded in paraffin blocks and cut into 4-μm sections. The sections were stained with hematoxylin and eosin (H&E; (cat. no. G1120; Beijing Solarbio Science & Technology Co., Ltd.) at room temperature for histological assessment. The slides were dewaxed and stained with ready-to-use hematoxylin for 3 min, then rinsed with distilled water for 5 min and differentiated with 1% hydrochloric acid alcohol for 10 sec, followed by washing in distilled water for 1 min. The slides were then stained with ready-to-use eosin (water-soluble) for 1 min followed by washing in distilled water for 20 sec. The H&E-stained sections were observed under a light microscope (Nikon Corporation).

The ascites (1,000 ml extracted during surgery) were placed in a centrifuge tube and centrifuged at 6,000 x g for 10 min at room temperature. After centrifugation, the supernatant was poured away. The cell sediment deposited at the bottom was smeared on a slide and fixed with 95% alcohol at room temperature for 30 min for H&E staining and microscopic observation, which was performed as aforementioned. In addition, the cell sediment formed by centrifugation was fixed with 95% alcohol for 1 h at room temperature and centrifuged at 6,000 x g for 10 min, at room temperature. The sediment was then poured out, wrapped in filter paper, dehydrated, dipped in paraffin wax and embedded to prepare cell wax blocks (4 μm). The wax blocks were cut into 4-μm sections and prepared for immunohistochemical staining as follows. After washing three times in 0.01 M PBS (pH 7.4) for 5 min each time at room temperature, the sections were incubated with 3% hydrogen peroxide at room temperature for 10 min. The sections were then washed a further three times with 0.01 M PBS (pH 7.4) for 5 min each time at room temperature. Antigen retrieval was performed with EDTA at 100˚C for 2.5 min followed by washing with PBS. The sections were then incubated with undiluted primary antibody at 37˚C for 60 min and ready-to-use secondary antibody at 37˚C for 20 min. The following primary antibodies were used: Ready-to-use primary antibodies against broad-spectrum cytokeratin (CK; cat. no. MAB-0671); vimentin (cat. no. MAB-0735); SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (INI-1; cat. no. MAB-0696); synaptophysin (Syn; cat. no. MAB-0742); calretinin (cat. no. MAB-0716); thyroid transcription factor-1 (TTF-1; cat. no. MAB-0677); SOX10 (cat. no. RMA-0726); CK7 (cat. no. MAB-0828); CK8/18 (cat. no. MAB-1002); NapsinA (cat. no. MAB-0704); CK20 (cat. no. MAB-0834), CDX-2 (cat. no. MAB-1056); special AT-rich sequence-binding protein 2 (SATB-2; cat. no. RMA-0750); Villin (cat. no. MAB-0710); GATA3 (cat. no. MAB-0695); P63 (cat. no. MAB-0694); CEA (cat. no. MAB-0852); Wilms tumor gene (WT-1; cat. no. MAB-0678); paired box gene 8 (PAX-8; cat. no. MAB-0837); CD34 (cat. no. Kit-0004); ERG (cat. no. RMA-0748); CD56 (cat. no. MAB-0743); desmin (cat. no. MAB-0766); myogenic differentiation 1 (MyoD1; cat. no. MAB-0822); epithelial membrane antigen (EMA; cat. no. Kit-0011); CD30 (cat. no. MAB-0868); S-100 (cat. no. Kit-0007); SMARCA4 (cat. no. RMA-1063); mutL homolog 1 (MLH1; cat. no. MAB-0838); mutS homolog 2 (MSH2; cat. no. MAB-0836); mutS homolog 6 (MSH6; cat. no. MAB-0831); postmeiotic segregation increased 2 (PMS2; cat. no. MAB-0859); P53 (cat. no. MAB-0674) and Ki-67 (cat. no. MAB-0672) (Fuzhou Maixin Biotech Co., Ltd.). Biotinylated goat anti-mouse and rabbit secondary antibodies (cat. no. KIT-9710) were obtained from Fuzhou Maixin Biotech Co., Ltd. Finally, tissue sections were stained with 3,3'-diaminobenzidine at room temperature for 5 min, counterstained with hematoxylin at room temperature for 5 min and images were captured using a light microscope (Nikon Corporation).

Next-generation sequencing (NGS) was performed to detect mutations in SMARCA4 using a kit from Yuanma Gene Technology (Beijing) Co., Ltd. DNA was extracted from the appropriate paraffin-embedded tumor tissue for high-throughput gene sequencing to evaluate gene mutations, base replacements, insertions, deletions, copy number changes and fusion/rearrangement patterns. A paraffin tissue DNA kit (cat. no. FFPE DNA; Amoy Diagnostics Co., Ltd.) was used

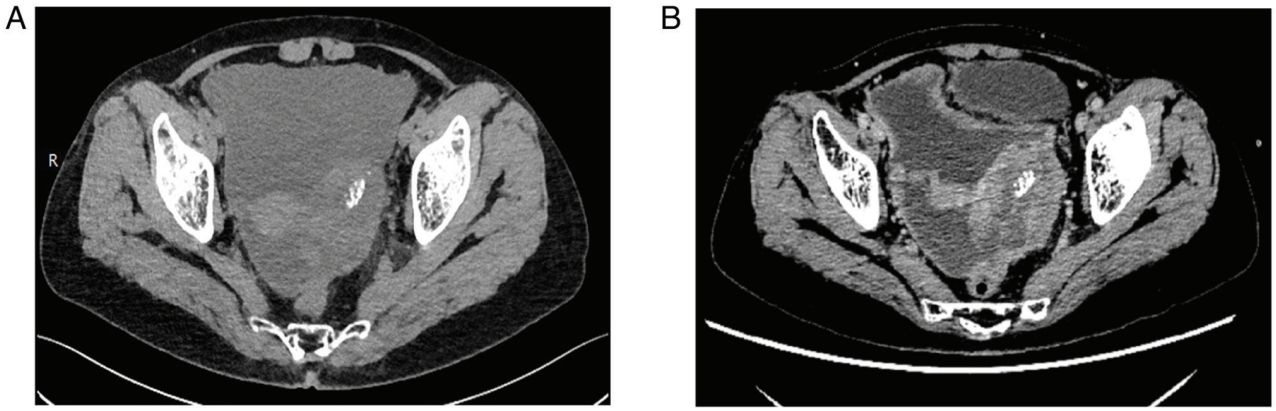

Figure 1. Computed tomography of the abdomen and pelvis. (A) Computed tomography and (B) enhanced computed tomography. Computed tomography showed soft tissue density in the left adnexal area, with spot-like high density, and a size of ~6.6x4.1 cm.

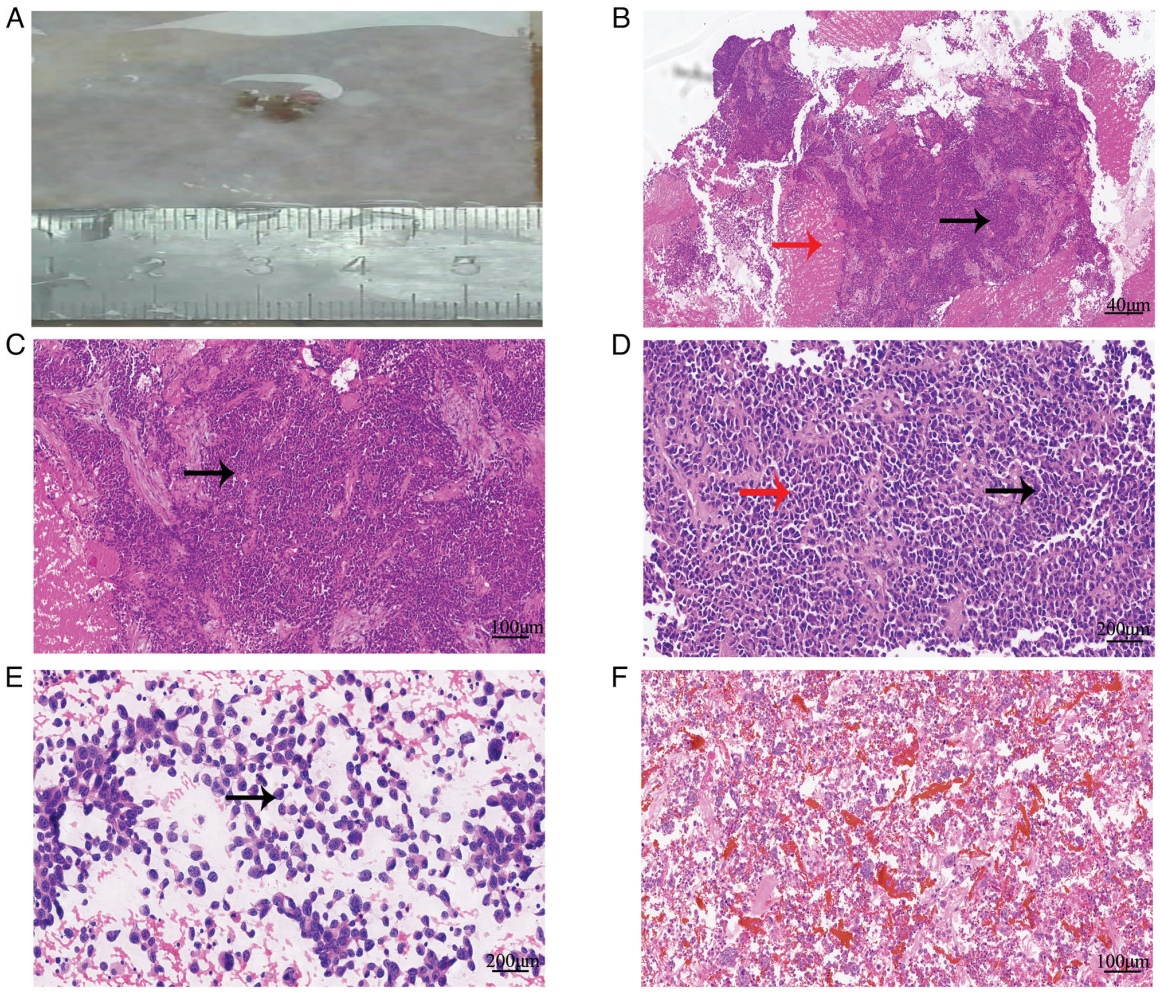

Figure 2. Histological features associated with the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4-deficient tumor in the adnexal area of the uterus. (A) Biopsied tissues of the lesions. (B) Histological morphology showed infiltrative growth of tumor cells, accompanied by necrosis (red arrow), tumor arrangement disorder and a local pseudochrysanthemum-like structure (black arrow) (hematoxylin and eosin, x40). (C) Tumor cells showed obvious atypia, diverse shapes (round and oval, black arrow) (hematoxylin and eosin, x100). (D) Tumor cells had clear nucleolus, abundant cytoplasm (black arrow), some cells had eosinophilic cytoplasm (red arrow), and mitotic figures were detected (hematoxylin and eosin, x200). (E) Smear of ascites tumor cells showed cytoplasmic eosinophilic cells (black arrow) (hematoxylin and eosin, x200). Cancer cells were observed in both (E) ascites smears and (F) cell blocks (hematoxylin and eosin, x100).

to extract DNA from the tumor sections. Subsequently, the extracted DNA concentration was measured with a spectrophotometer. The DNA concentration used for sequencing was 20 pM. The tumor exome was sequenced by high-throughput sequencing using the kit [cat. no. YMFW-102; Yuanma Gene Technology (Beijing) Co., Ltd.]. Paired-end sequencing

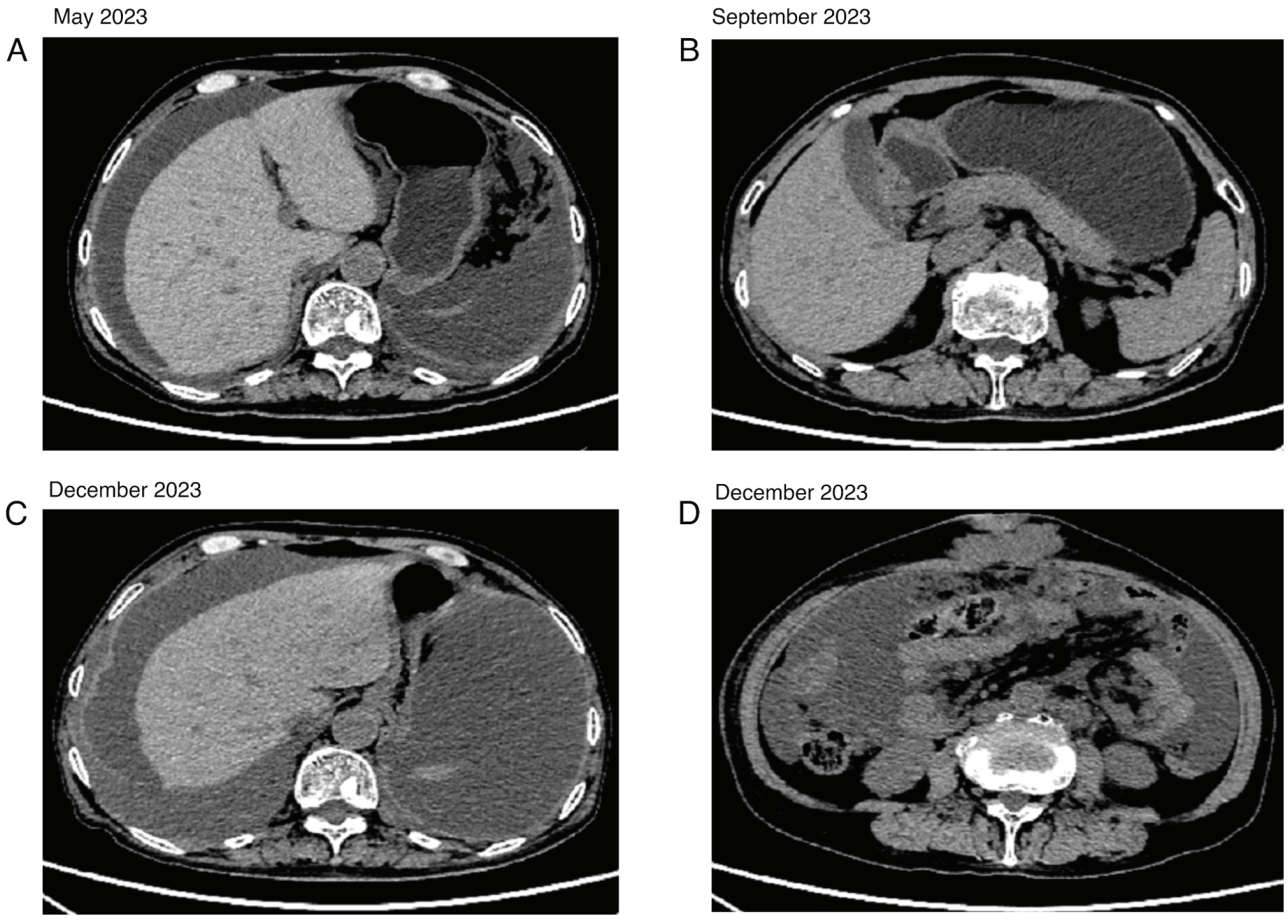

Figure 3. Changes in the computed tomography of the abdomen during treatment. (A) In May 2023, computed tomography showed ascites. (B) In September 2023, computed tomography exhibited reduced ascites. (C) In December 2023, computed tomography showed more ascites (compared with September 2023). (D) In December 2023, computed tomography showed multiple organ lesions.

was performed and the nucleotide length was 150-600 bp. Finally, the data were analyzed using trimmomatic software (version: 0.38; http://www.usadellab.org/cms/index.php?page=trimmomatic).

Morphological and immunohistochemical findings, and the results of NGS analysis. Microscopically, tumor cells showed infiltrative growth with local pseudochrysanthemum-like structures accompanied by necrosis. The tumor cells showed obvious atypia and diverse shapes, such as round and oval nuclei, and abundant cytoplasm, and some of the cells had eosinophilic cytoplasm and mitotic figures. Cancer cells were observed in both ascites smears and cell blocks (Fig. 2B-F). Immunohistochemically, the tumor cells showed positive expression of vimentin (Fig. 4A), INI-1 (Fig. 4C) and Syn (Fig. 4B), and scattered expression of CK, TTF-1, SOX10 and CK7; the tumor was negative for CK8/18, NapsinA, CK20, CDX-2, SATB-2, Villin, GATA3, P63, CEA, WT-1, PAX-8, CD34, ERG, CD56, desmin, MyoD1, calretinin, EMA, CD30, S-100 and SMARCA4 (Fig. 4D). Mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) were positive. P53 was negative. The Ki-67 index of the tumor cells was ~85% (Fig. 4E). Notably, with the exception of vimentin, INI-1, Syn, SMARCA4 and Ki-67, the images of immunohistochemical staining are not shown.

The NGS results showed no SMARCA4 gene mutation, a TP53 gene frameshift deletion and a Fanconi anemia protein A (FANCA) gene missense mutation (exon 33 p.S1088F) (Table SI). Other gene mutations were negative.

Based on the aforementioned clinical information, morphological features and immunohistochemical results, the pathological diagnosis was primary SMARCA4-deficient tumor in the adnexal region.

Discussion

SMARCA4 is on chromosome 19q13.2 and is one of two catalytic subunits of the SWI/SNF complex. Deletion or mutation of the catalytic and core subunits of the SWI/SNF complex in somatic cells or germline backgrounds can result in inactivation of coding proteins and an abnormal overall function of the complex. The SWI/SNF complex is a key component of chromatin remodeling, which can bind to nucleosomes and use the energy of ATP to disrupt DNA and histone interactions, move or eject histones, alter nucleosome structure, and alter transcription and regulatory mechanisms, leading to tumorigenesis (7,8). Peng *et al* (1) reported that SMARCA4 expression was significantly higher in various malignant solid tumors than in normal tissues, whereas its expression level in renal clear cell carcinoma and eosinophilic renal tumors was revealed to be significantly

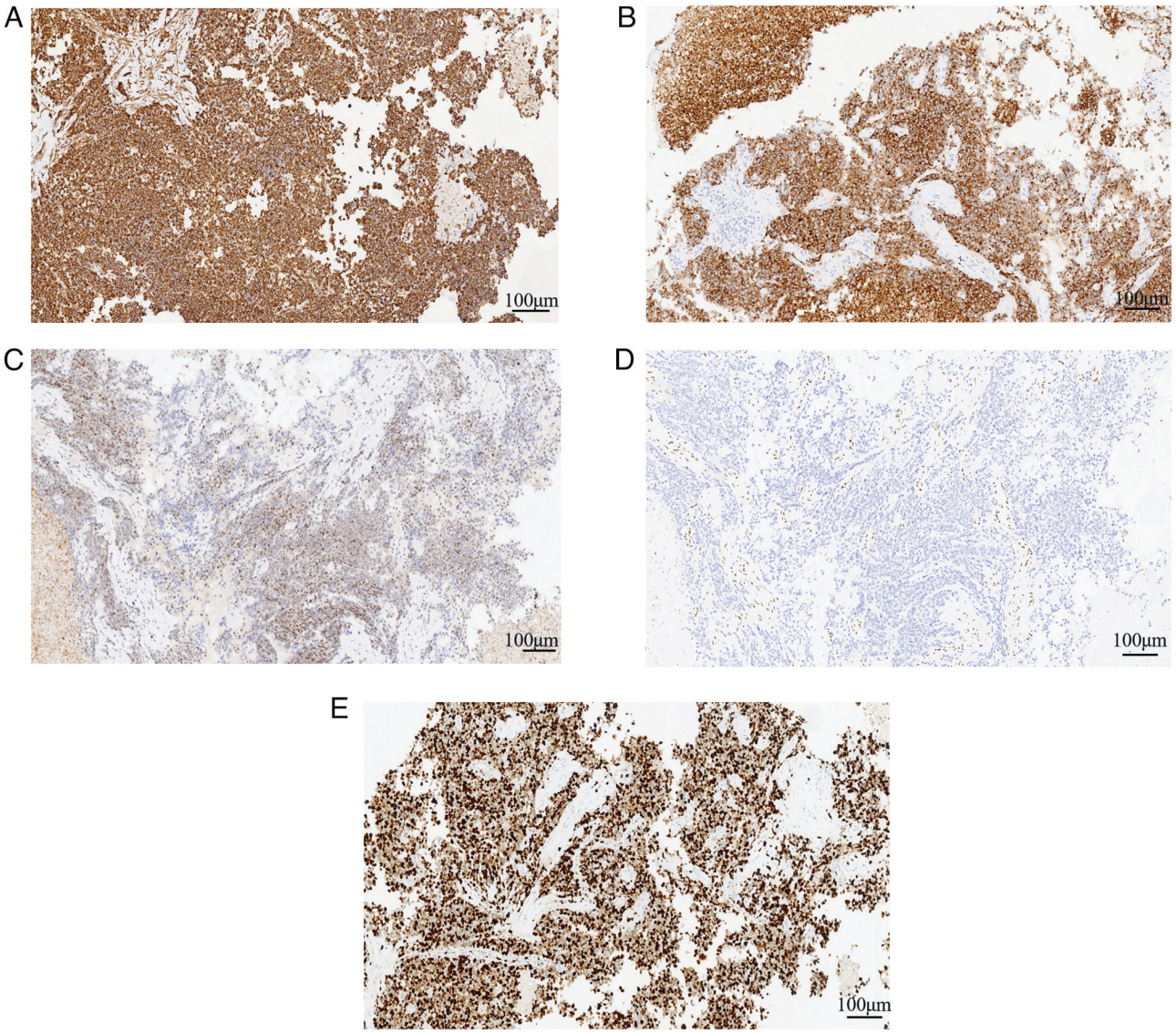

Figure 4. Immunohistochemistry of SMARCA4-deficient tumor in the adnexal area of the uterus. Immunohistochemical staining of (A) vimentin, (B) synaptophysin and (C) SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 was diffuse in the tumor cells (x100). (D) Negative expression of SMARCA4. (E) Ki-67 index of tumor cells was ~85% (x100). SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4.

lower than that in normal tissues. SMARCA4-deficient tumors are common in non-small cell lung cancer, colorectal adenocarcinoma, bladder urothelial carcinoma and invasive breast ductal carcinoma, and are associated with a poor prognosis (9).

The most commonly observed tumors with SMARCA4 mutations in the female reproductive system are small cell carcinoma of the ovary hypercalcemic type (SCCOHT) (10), undifferentiated and dedifferentiated endometrial carcinoma, and SMARCA4-deficient undifferentiated tumors of the uterus (11). SMARCA4-mutated tumors in the female reproductive system are often clinically asymptomatic, present with abdominal pain and distension, and are confirmed using imaging data and pathological examination (12,13). Because of the aggressive nature of SMARCA4-deficient tumors, they are often treated in the middle and late stages, and their progression is rapid. Microscopically, these tumors are distributed in sheets or nests, with epithelioid and rhabdomyoid morphology. Mitotic figures are easily observed, with large necrosis and loss of SMARCA4 expression. Due to differences in tumor treatment and prognosis, adnexal SMARCA4-deficient tumors must be differentiated from ovarian SCCOHT and high-grade serous carcinoma. SCCOHT is most common in adolescents and young women, occurring at a mean age of 24 years, and is associated with elevated blood calcium levels. The tumor cells are generally small, round and uniform in size, and are arranged in sheets, nests, islands, beams or ropes, similar to neuroendocrine cells. Cases showing large cells in the tumor are referred to as macrocellular SCCOHT (14). The SCCOHT tumor cells are often positive for expression of EMA, CK and neuroendocrine markers (CD56, CgA and Syn). However, unilateral or bilateral SCCOHT is more common in middle-aged and older women. The high-grade serous carcinoma tumor is solid, papillary, glandular or cribriform, and the tumor cells are pleomorphic with obvious atypia and mitotic figures. Immunohistochemistry has shown that WT-1 is positive and P53 is mutated in high-grade serous carcinoma. Table I shows the differential diagnosis of

Table I. Differential diagnosis of SMARCA4-deficient adnexal tumors from SCCOHT and high-grade serous carcinoma.

Tumor Type	Blood Common age	calcium level	Microscopic appearance	Tumor expression								(Refs.)
				CK	Vimentin	CD56	CgA	Syn	P53	WT-1	SMARCA4	
SMARCA4-deficient tumors	No consensus	Normal	Lamellar and/or nest-like distribution, with epithelioid and rhabdomyoid morphology, mitotic figures are visible, and necrosis is often detected.	+/-	+	-	-	+/-	No consensus	-	-	(11,13)
SCCOHT	Under 40 years old	High	Similar neuroendocrine cells of uniform size arranged in sheets, nests, islands, beams or cords.	+	-	+	+	+	No mutation	-	+/-	(12)
High-grade serous carcinoma	Middle-aged and elderly	Normal	Solid, papillary, glandular or cribriform structure; cells are polymorphic and heteromorphic, mitotic figures are obvious.	+	-	-	-	-	Mutated	+	+	(14,15)

SCCOHT, small cell carcinoma of the ovary hypercalcemic type; SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4; CK, cytokeratin; Syn, synaptophysin; WT-1, Wilms tumor gene.

adnexal SMARCA4-deficient tumors from SCCOHT of the ovary and high-grade serous carcinoma (15).

SMARCA4 mutations are mainly stop/nonsense, frameshift, splicing and missense mutations, and in-frame deletions, and no specific mutation site has been defined (16-19). Uterine SMARCA4-deficient tumors show the highest frequency of SMARCA4 mutations, whereas the SMARCA4-amplified type is the main form of ovarian cancer, with a frequency of 9% (1). In the present case, the NGS results showed that no SMARCA4 mutation was detected, whereas the FANCA gene contained a missense mutation. SMARCA4 mutations lead to a loss of SMARCA4, which can be detected using immunohistochemical methods (1). Mutations in SMARCA4 are often accompanied by TP53 mutations. In the present case, immunohistochemistry showed that SMARCA4 protein expression was absent, and the NGS sequencing results indicated that SMARCA4 was not mutated, possibly because of structural variations in the intron region of the gene or mutations in other proteins of the SWI/SNF family. Additionally, a frameshift deletion of TP53 was detected. FANCA, a homologous recombination repair pathway gene, encodes Fanconi anemia protein A and belongs to the Fanconi anemia family. The most common changes in FANCA in cancer have been reported to be FANCA mutations (2.31%), FANCA loss (0.24%), FANCA nonsense mutations (0.14%), FANCA frameshift mutations (0.10%) and FANCA amplifications (0.07%) (20). FANCA changes occur in 2.82% of malignant solid tumors and in 2.22% of patients with ovarian cancer. Notably, loss of FANCA function is associated with hereditary breast and ovarian cancer (21,22).

Currently, there is no consensus on the best treatment plan for SMARCA4-mutated tumors, and radical surgery, chemotherapy and radiotherapy can be used as treatment methods. Anti-programmed cell death-1/programmed cell death-ligand 1 immunotherapy has a curative effect on SMARCA4-deficient thoracic tumors and SMARCA4-deficient undifferentiated tumors of the gastrointestinal tract (23,24). Additionally, immunosuppressive targets, such as monoclonal antibodies against programmed death receptor 1 and programmed death ligand 1, suitable for immunotherapy combined with chemotherapy (platinum and/or paclitaxel) were revealed to be effective for treating SMARCA4-deficient undifferentiated thoracic tumors (21,25). Perioperative and palliative radiotherapy may

improve the prognosis of patients with SMARCA4-deficient undifferentiated uterine sarcomas (24). In cases where standard therapy does not work, novel therapies, such as enhancer of zeste homolog inhibitors (21) and etoposide, as well as targeted therapy with histone deacetylase inhibitors and DNA methyltransferase inhibitors, may be considered (25). Another case report showed that application of a poly ADP-ribose polymerase inhibitor was beneficial for treating recurrent epithelial ovarian cancer with a FANCA mutation (26). Most patients with SMARCA4-deficient undifferentiated tumors are diagnosed in the advanced stages, with rapid progression and poor prognosis, whereas patients with lymph node metastasis of SMARCA4-deficient undifferentiated tumors have a worse prognosis with a median overall survival of 4-6 months (27).

Since the discovery of SMARCA4-deficient tumors in recent years, no consensus has been reached on the diagnostic criteria or treatment plan for this type of cancer. The present case report provides relevant evidence for such tumors occurring in the adnexal region of the uterus. Data on a larger number of cases should be collected to improve the understanding of this disease and improve prognosis.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article. The NGS data generated in the present study may be found in the BioProject database under accession number PRJNA1102919 or at the following URL: https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1102919.

Authors' contributions

XFL and MQY confirm the authenticity of all the raw data. XFL was responsible for funding acquisition. XFL, YPZ, LLW, ZJW and MQY designed the study. XFL, MQY and ZJW were responsible for writing the original draft. XFL, MQY and ZJW were responsible for editing the original draft. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The research protocol was reviewed and conducted with the approval of the local institutional review board at the Weifang People's Hospital (First Affiliated Hospital of Shandong Second Medical University; Weifang, China; approval no. KYLL20240105-2). The patient provided written consent to participate in the study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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