

DNA polymerase ϵ -mutant endometrial carcinosarcoma: A case report and literature review

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Received September 11, 2025; Accepted September 25, 2026

DOI: 10.3892/etm.2026.13340

Abstract. DNA polymerase ϵ (POLE)-mutant endometrial carcinosarcoma (ECS) is a rare clinical lesion. The current study describes the diagnosis and treatment of a woman who presented with yellow vaginal discharge for >2 months; in addition, a literature review was conducted, and the clinical and pathological characteristics, treatment and prognosis of POLE-mutant ECS are discussed. Preoperative endometrial curettage was performed and the patient was diagnosed with poorly differentiated adenocarcinoma. Based on this finding, a total hysterectomy, bilateral adnexectomy and lymph node dissection were performed. A postoperative pathological examination revealed the morphological characteristics of a high-grade carcinosarcoma in the endometrial tumor. The results of immunohistochemical staining showed that the carcinoma was cytokeratin 7-positive (sarcoma, -) and both the carcinoma and sarcoma were vimentin-positive (carcinoma, weak +; sarcoma, +). Additionally, TP53 showed aberrant immunohistochemical overexpression in the carcinoma and sarcoma, and the Ki-67 proliferation index was 80% in carcinosarcoma. Molecular testing revealed a c.1231G>T (p.Val411Leu) mutation in exon 13 of the POLE gene, and mutations in the TP53 gene were detected in exons 5, 6 and 8. Adjuvant therapy was not administered to the patient after surgery, and no recurrence/metastasis was detected during the 18-month follow-up period. These findings indicate that molecular subtyping should be performed routinely in ECS to identify the POLE-mutant subtype and to avoid overtreatment.

Introduction

Endometrial carcinosarcoma (ECS) is a rare high-grade malignant tumor of the uterus, which exhibits both epithelial

carcinoma and mesenchymal sarcoma components. The fifth edition of the World Health Organization (WHO) classification categorizes ECS as a subtype of endometrial carcinoma, which accounts for ~5% of all uterine malignant tumors (1,2). ECS has a high degree of malignancy and a 5-year survival rate of 33-39% in the United States (3). After the molecular classification of endometrial cancer was conducted in 2013, molecular pathological studies found that 7-12% of endometrial cancer cases have mutations in the DNA polymerase ϵ (POLE) gene. These tumors exhibit an ultra-high mutational phenotype and demonstrate a markedly better prognosis compared with the other three TCGA molecular subtypes of endometrial carcinoma (4-6). Furthermore, the ratio of microsatellite stability to TP53 mutation has been reported to be 1.9:1 in POLE-mutant endometrial cancer (7). In the absence of molecular typing, POLE-mutant endometrial cancer with good prognosis may be misinterpreted as invasive endometrial cancer, which has an unfavorable prognosis.

To the best of our knowledge, POLE-mutant ECS has rarely been reported (8-11). In 2025, Toboni *et al* (10) reported that among 2,235 cases of ECS, 48 cases (48/2,235; 2.1%) were POLE-mutant. The prognoses of the patients with POLE-mutant ECS were considerably improved compared with those of the patients with the TP53-abnormal (TP53-mutant molecular subtype) ECS (median overall survival, 74.8 vs. 21.9 months, respectively). Therefore, correctly screening POLE-mutant ECS by molecular typing is important for effective treatment. The present study reports a case of POLE-mutant ECS diagnosed via molecular detection, and discusses its diagnosis and treatment strategy based on previous studies. The current findings may serve as a reference for clinicians and pathologists.

Case report

Clinical presentation. A female patient (age, 61 years), whose menopause occurred prior to admission, was admitted to The Second People's Hospital of Xiaoshan District (Hangzhou, China) in February 2025, after experiencing yellow vaginal discharge for >2 months. A gynecological examination revealed that the vulva was intact. The patient had a history of childbirth; their vagina appeared smooth, and their uterus was in an anterior position, of normal size, medium texture, non-tender and with acceptable mobility. No obvious mass or tenderness was detected in the bilateral ovarian and fallopian

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Key words: endometrial cancer, carcinosarcoma, DNA polymerase ϵ gene mutation, molecular typing, treatment, prognosis

tube regions. A human papillomavirus test of cervical cell samples showed positive results for subtype 52, and the cervical liquid-based cytology examination (Shijiazhuang New Century Engineering Co., Ltd.) showed no intraepithelial lesions or malignant cells. Gynecological B-ultrasound examination showed that the uterus was clear, with a slightly stronger heterogeneous echo mass of 4.3x2.9x4.1 cm in size in the uterine cavity, low-resistance blood flow signals and no prominent endometrium. Pelvic magnetic resonance imaging, plain scan and functional imaging showed abnormal signals in the uterine cavity measuring 4.2x3.1 cm; the boundary between the lesion and the muscular layer was well-defined and a malignant tumor was considered (Fig. 1). No abnormal signal shadow was found in the cervix, bilateral ovarian and fallopian tube regions, and uterorectal fossa. The bladder and pelvic wall had a normal structure, and the lymph nodes in the pelvic cavity were not enlarged. The patient had a body mass index of 22.7 kg/m² (within the normal healthy range for Chinese adults). The patient had two sons and one daughter; obstetric history was recorded using the TPAL system (3-0-0-3: term-preterm-abortion-living children). Notably, the patient had undergone surgical repair of a perforated gastric ulcer >10 years ago and had lived with chronic hepatitis B for >50 years without complications. Abdominal B-ultrasound examination showed no prominent masses in the liver, kidney or retroperitoneal space, and no tumors were detected using head and chest computed tomography. Serological test results showed that carcinoembryonic antigen (CEA; reference range, 0-5 ng/ml), cancer antigen (CA)199 (reference range, 0-37 U/ml), CA125 (reference range, 0-30.2 U/ml), α -fetoprotein (AFP; reference range, 0-8.1 ng/ml) and squamous cell carcinoma-associated antigen (SCC-Ag; reference range, 0-1.5 ng/ml) levels were within normal limits. Diagnostic curettage was performed 3 days after admission. The obtained intrauterine tissue specimens were fixed in 10% neutral-buffered formalin at room temperature (25°C) for 24 h, embedded in paraffin, sectioned and stained with haematoxylin-eosin (H&E). Histopathological examination of curettage material yielded a diagnosis of poorly differentiated adenocarcinoma of the uterine cavity. The patient underwent laparoscopic hysterectomy, bilateral ovariectomy and salpingectomy, para-aortic lymph node resection and pelvic lymph node dissection under general anesthesia. The surgical size of the uterus was 6.5x5.5x5.5 cm. The cervix was atrophic with a smooth surface, the length of the cervical canal was 2 cm and the endometrial thickness was 0.1 cm. A 4.0x4.0x2.0 cm exogenic gray-yellow soft mass was located near the uterine horn on the right side of the uterus, with a gray-yellow, fish-meat-like cut surface and a gelatinous area infiltrating the superficial muscle layer. No notable abnormalities were detected in the bilateral ovaries and fallopian tubes.

Resected uterine tumor tissue was fixed with 10% neutral formalin at room temperature (25°C) for 24 h, embedded in paraffin, cut into sections (3 μ m) and stained with H&E. H&E staining was performed at room temperature (25°C): Hematoxylin for 5 min and 1% aqueous eosin for 1 min. Slide observation was carried out using a bright-field light microscope. Microscopic examination showed that the tumor consisted of intermingled carcinoma and sarcoma components (Fig. 2). The epithelial components included

endometrioid carcinoma (FIGO grade 3, 10%) (Fig. 3), mucinous adenocarcinoma (FIGO grade 3, 30%) (Fig. 4), and a high-grade undifferentiated sarcoma characterized by spindle and small round cells (60%) (Figs. 5 and 6) (1). The tumor invaded the myometrium (<1/2) without lymphovascular space invasion (LVSI).

Immunohistochemistry (IHC) analysis was performed using an EnVision IHC kit (polymer method; cat. no. KIT-0014; Fuzhou Maixin Biotechnology Development Co., Ltd.) using primary antibodies (incubated for 50 min at 25°C) purchased from Beijing Zhongshan Jinqiao Biological Co., Ltd. and Fuzhou Maixin Biotechnology Development Co., Ltd., to target the following proteins (pre-diluted working solutions unless otherwise indicated): Cytokeratin (CK)7 (1:100; cat. no. 21022407), Cam5.2 (working fluid; cat. no. 19121791), estrogen receptor (ER) (1:200; cat. no. 6072353), progesterone receptor (PR) (1:400; cat. no. 9071722), vimentin (Vim) (1:100; cat. no. 21031351), paired box gene 8 (Pax-8) (1:100; cat. no. 21012350), p16 (working fluid; cat. no. 2107210673d), TP53 (p53) (1:100; cat. no. 20082125), SMARCA4 (BRG1) (working fluid; cat. no. 21045528), MutL homolog 1 (MLH1) (1:100; cat. no. 2109290789d), MutS Homolog 2 (MSH2) (1:200; cat. no. 2104220836C2), MutS Homolog 6 (MSH6) (1:200; cat. no. 2101280831C1), Mismatch repair endonuclease PMS2 (PMS2) (1:100; cat. no. 2109150775d), NapsinA (1:100; cat. no. 20091108), CerbB-2 (working fluid; cat. no. H13317) and Ki-67 proliferation index (Ki-67) (1:200; cat. no. 20091812). IHC sections were observed under a light microscope without software analysis.

The results were as follows: CK7 (carcinoma, +; sarcoma, -) (Fig. 7A), Cam5.2 (carcinoma, +; sarcoma, -) (Fig. 7B), estrogen receptor (carcinoma, 10% +; sarcoma, -) (Fig. 7C), progesterone receptor (carcinoma, 1% +; sarcoma, -) (Fig. 7D), vimentin (carcinoma, weak +; sarcoma, +) (Fig. 7E), paired box gene 8 (carcinoma, +; sarcoma, partial +) (Fig. 7F), P16 (+) (Fig. 7G), TP53 (mucinous adenocarcinoma and small round cell sarcoma showed aberrant immunohistochemical overexpression; Figs. 7H and I), SMARCA4 (+) (Fig. 8A), MLH1 (+) (Fig. 8B), MSH2 (+) (Fig. 8C), MSH6 (+) (Fig. 8D), PMS2 (+) (Fig. 8E), NapsinA (-) (Fig. 8F), CerbB-2 (1+) (Fig. 8G), desmin (-) (Fig. 8H) and Ki-67 proliferation index (80%) (Fig. 8I) (Table I). Consequently, the primary pathological diagnosis was identified as ECS (TP53-abnormal type), which invaded less than one-half of the myometrium. LVSI was not detected and all 39 resected lymph nodes were negative for metastatic tumor cells. The tumor was classified as FIGO 2023 stage IIC endometrial carcinoma (1).

Molecular testing methods. Molecular testing was performed by the Molecular Laboratory of Hangzhou Adicon Medical Laboratory Center Co., Ltd. (Zhejiang, China) using next-generation sequencing (NGS) technology on the GeneMind SURFSeq 5000 sequencing system (ref. genome, GRCh37/hg19). This SURFSeq 5000 system is used as described in the sequencing details below.

Sample preparation reagents and quality control methods. Details of the reagents used for sample preparation are described below. Specifically, for genomic DNA extraction from formalin-fixed paraffin-embedded (FFPE) samples,

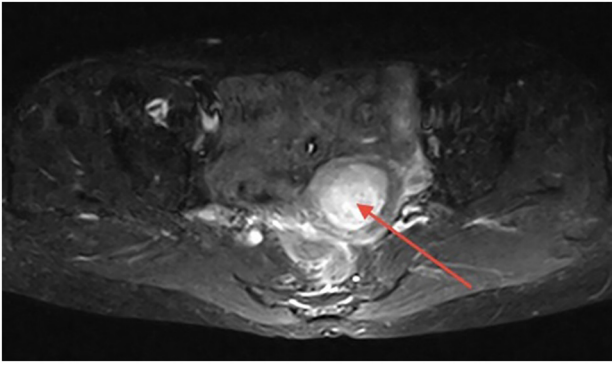


Figure 1. Magnetic resonance imaging plain scan and functional imaging showed abnormal signals in the uterine cavity measuring 4.2x3.1 cm (red arrow), and the boundary between the lesion and the muscular layer was well-defined.

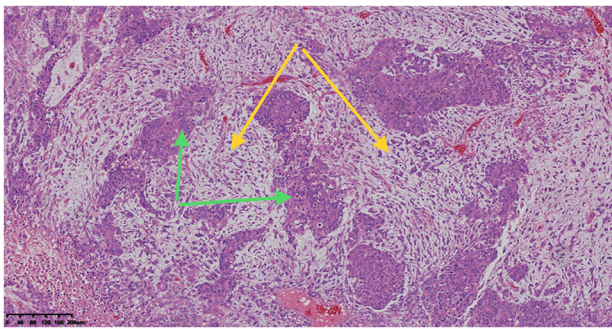


Figure 2. Microscopically, the tumor was composed of carcinoma (green arrow) and sarcoma (yellow arrow) components (magnification, x100; scale bar, 200 μ m; H&E staining).

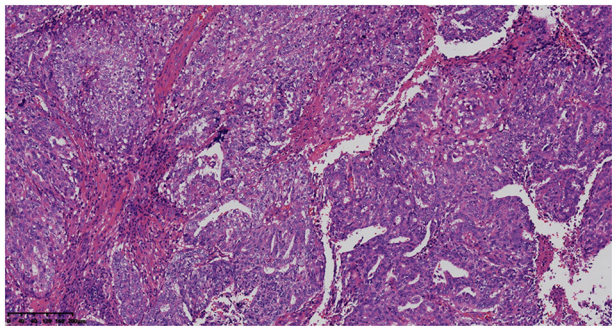


Figure 3. High-grade endometrioid carcinoma with necrosis (magnification, x100; scale bar, 200 μ m; H&E staining).

the FastPure FFPE DNA Isolation Kit (cat. no. DC105-01; Vazyme Biotech Co., Ltd.) was used. DNA concentration was quantified using the Qubit fluorometer (Thermo Fisher Scientific, Inc.). DNA integrity and fragment size distribution were assessed using the Fragment Analyzer system (Agilent Technologies, Inc.). Library preparation was conducted using the Adicon LDT Solid Tumor Mini panel (Twist Bioscience). For library construction, the required reagents consisted of enzymes for DNA fragmentation and end repair (fragmentation enzyme, T4 DNA polymerase; Klenow fragment, T4 polynucleotide kinase), enzymes for A-tailing and adapter ligation [Klenow fragment (3'-5' exo-) and T4 DNA ligase],

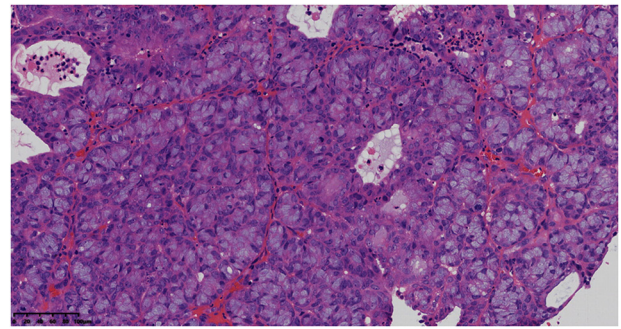


Figure 4. Mucinous adenocarcinoma region (magnification, x200; scale bar, 100 μ m; H&E staining).

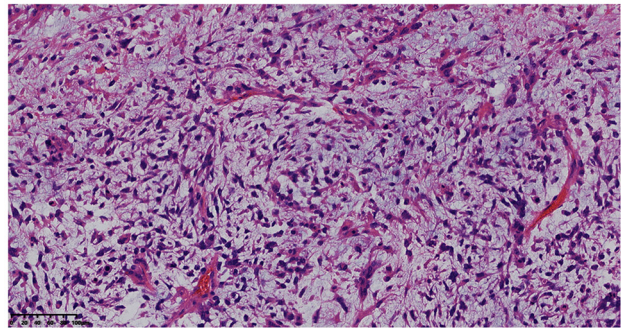


Figure 5. Spindle cell sarcoma region, in which cell atypia was prominent; the stroma was loose and mucous degeneration was detected (magnification, x200; scale bar, 100 μ m; H&E staining).

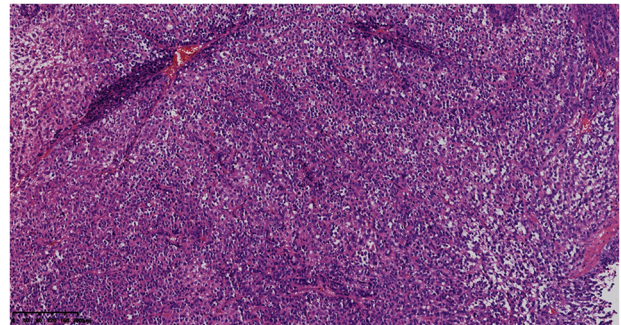


Figure 6. Primary small round cell sarcoma region (magnification, x100; scale bar, 200 μ m; H&E staining).

dual-indexed sequencing adapters (with unique molecular identifiers), high-fidelity DNA polymerase, a dNTP mix (dATP, dTTP, dCTP, dGTP) and a primer mix (for library amplification). Hybridization was performed using the Twist Fas Hybridization Reagents Kit (Twist Bioscience). For hybridization, the core reagents included biotinylated DNA capture probes (120-150 bp), Human Cot-1 DNA, universal blocking oligos (serving as blocking agents), a high-salt hybridization buffer containing formamide, low-stringency wash buffer (2X SSC; 0.1% SDS), high-stringency wash buffer (0.1X SSC; 0.1% SDS), streptavidin-coated magnetic beads and elution buffer (0.1 M NaOH or Tris-HCl). In addition, quality control reagents, including fragment analyzer reagents, were used in the process to ensure the reliability of the experiment. The

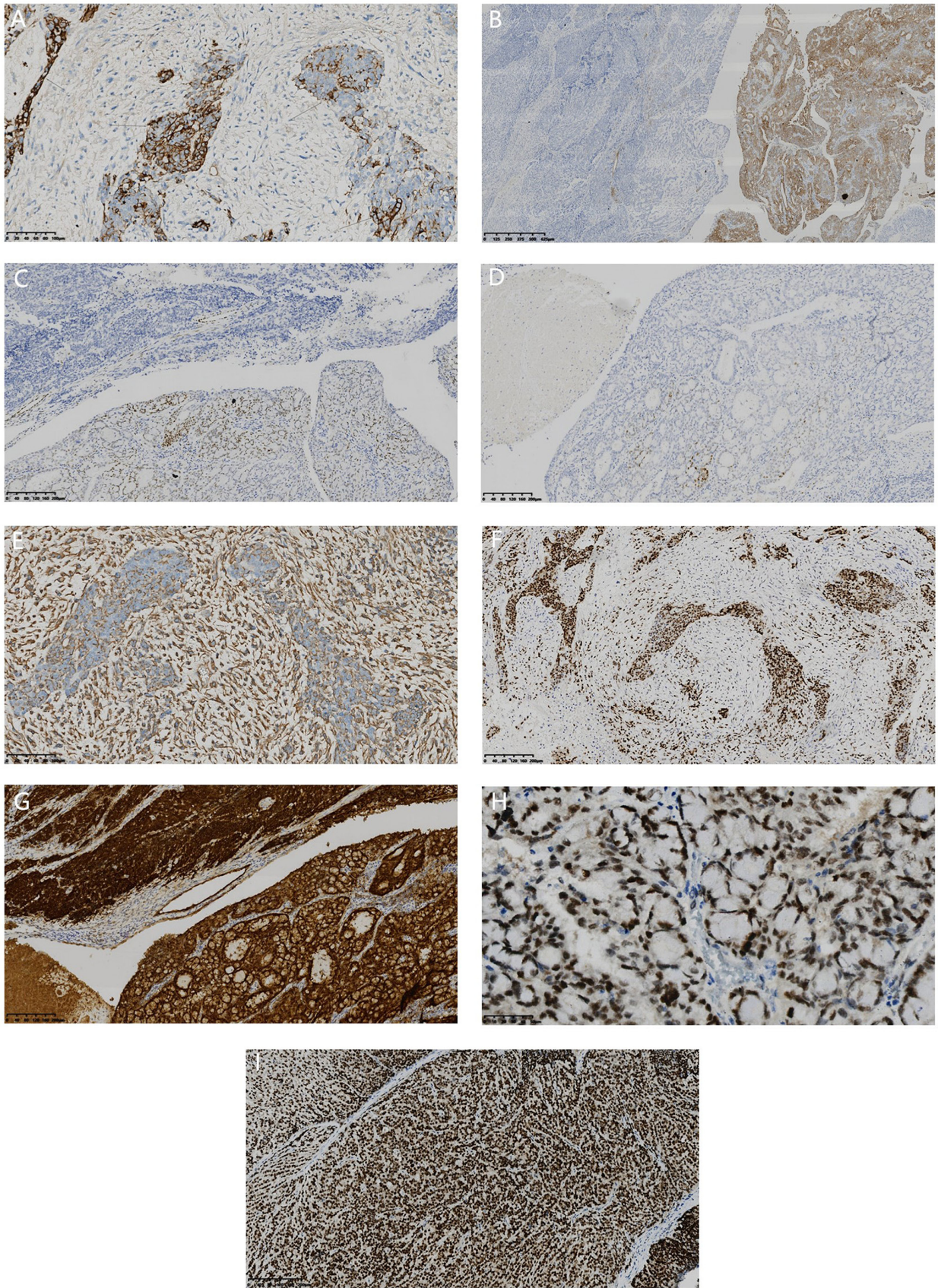


Figure 7. Immunohistochemical staining. (A) Cytokeratin 7 expression (carcinoma, + (arrow); sarcoma, -) (magnification, x200; scale bar, 100 μ m). (B) Cam5.2 expression (carcinoma, +; sarcoma, -) (magnification, x32; scale bar, 625 μ m). (C) Estrogen receptor expression (carcinoma, 10% +; sarcoma, -) (magnification, x100; scale bar, 200 μ m). (D) Progesterone receptor expression (carcinoma, 1% +; sarcoma, -) (magnification, x100; scale bar, 200 μ m). (E) Vimentin expression (carcinoma, weak +; sarcoma, +) (magnification, x200; scale bar, 100 μ m). (F) Paired box gene 8 expression (carcinoma, +; sarcoma, partial +) (magnification, x100; scale bar, 200 μ m). (G) p16 expression (+) (magnification, x100; scale bar, 200 μ m). (H) p53 aberrant immunohistochemical overexpression in mucinous adenocarcinoma (magnification, x400; scale bar, 50 μ m). (I) p53 aberrant immunohistochemical overexpression in small round cell sarcoma (magnification, x100; scale bar, 200 μ m).

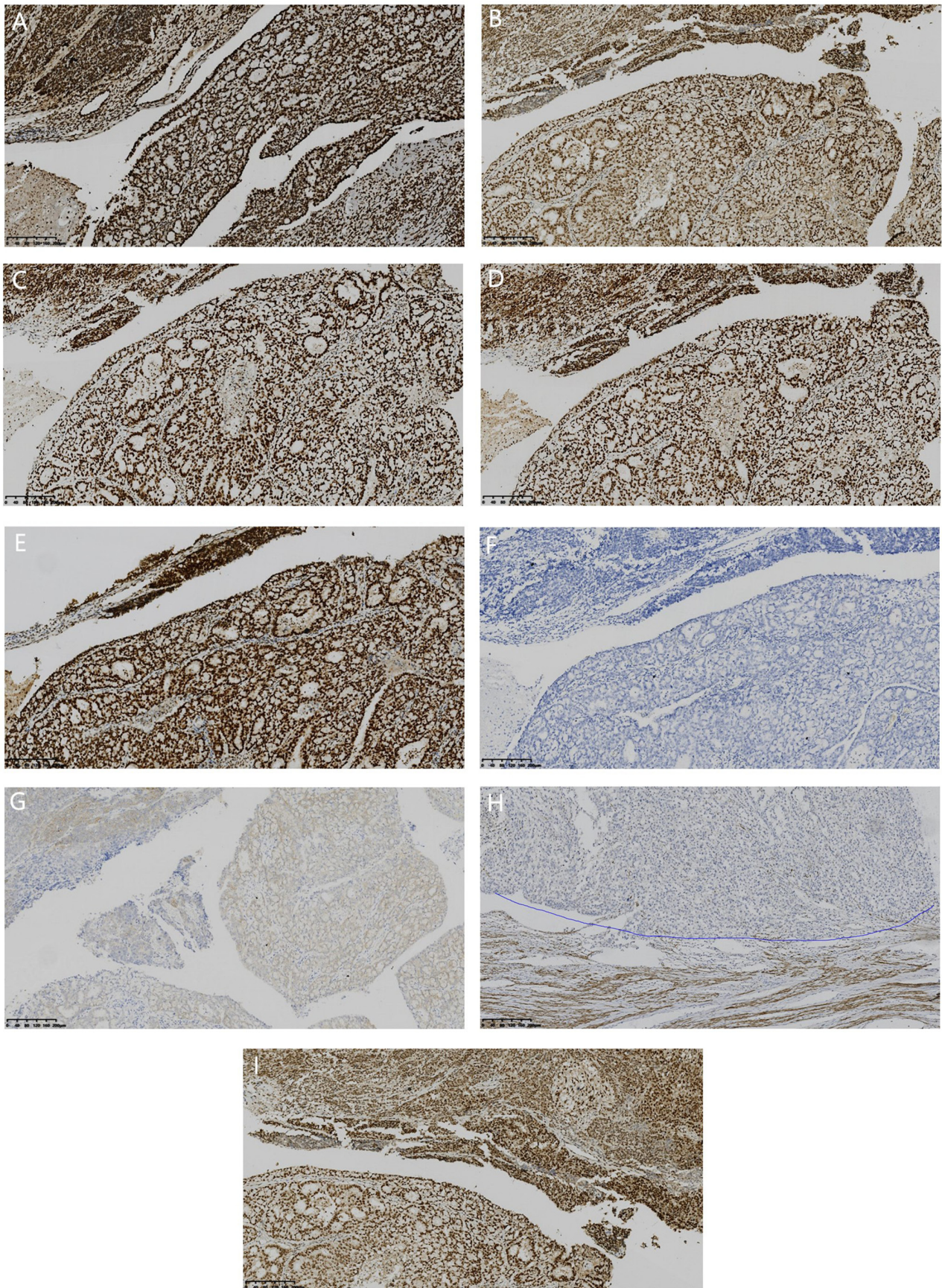


Figure 8. Immunohistochemical staining. (A) SMARCA4 expression (+) (magnification, x100; scale bar, 200 μ m). (B) MutL homolog 1 expression (+) (magnification, x100; scale bar, 200 μ m). (C) MutS Homolog 2 expression (+) (magnification, x100; scale bar, 200 μ m). (D) MutS Homolog 6 expression (+) (magnification, x100; scale bar, 200 μ m). (E) Mismatch repair endonuclease PMS2 expression (+) (magnification, x100; scale bar, 200 μ m). (F) NapsinA expression (-) (magnification, x100; scale bar, 200 μ m). (G) CerbB-2 (1+) expression (magnification, x100; scale bar, 200 μ m). (H) Desmin expression (-) (above the blue line. The tumor tissue was negative, while the smooth muscle tissue of the internal control was positive.) (magnification, x100; scale bar, 200 μ m). (I) Ki-67 proliferation index of 80% (magnification, x100; scale bar, 200 μ m).

Table I. Immunohistochemical staining results of endometrial carcinosarcoma.

Tumor name	ER	PR	Pax8	CK7	Cam5.2	Vim	Desmin	P16	SMARCA4	TP53	NapsinA	CerbB-2	MSH2	MLH1	PMS2	MSH6
Carcinoma	10%P	1%P	P	P	P	WP	N	P	P	MAO	N	1+	P	P	P	P
Sarcoma	N	N	PP	N	N	P	N	P	P	SRCSO	N	1+	P	P	P	P

P, positive; N, negative; PP, partially positive; W, weak; MAO, mucinous adenocarcinoma aberrant immunohistochemical overexpression; SRCSO, small round cell sarcoma aberrant immunohistochemical overexpression; ER, estrogen receptor; PR, progesterone receptor; Pax 8, paired box gene 8; CK7, cytokeratin 7; Vim, vimentin; MSH, mutS homolog; MLH1, mutL homolog 1; PMS2, mismatch repair endonuclease PMS2.

SURFSeq 5000 Sequencing Kit V2.0 (FCH 300 cycles) (cat. no. S000369; GeneMind Biosciences Co., Ltd.) was used for sequencing.

Sequencing details. i) Sequencing type: Paired-end NGS with a read length of 2x150 bp; ii) sequencing platform: SURFSeq 5000 (GeneMind Biosciences); iii) final library loading concentration and quantification: The final library was loaded at a concentration of 1 nM and quantified by the Qubit assay (Thermo Fisher Scientific).

Bioinformatic analysis. Raw sequencing reads were trimmed to remove adapters and low-quality bases using Cutadapt (v4.1, <https://github.com/marcelm/cutadapt>). Clean reads were aligned to the human reference genome GRCh37/hg19 (UCSC Genome Browser; <https://hgdownload.soe.ucsc.edu/goldenPath/hg19/>) with BWA-MEM (v0.7.17; <https://bio-bwa.sourceforge.net/>). PCR duplicates were marked by Picard (v2.27.5; Broad Institute; <https://github.com/broadinstitute/picard>). Base quality recalibration and somatic variant calling were performed using GATK (v4.2.6.1; Broad Institute; <https://gatk.broadinstitute.org/>). Detected variants were functionally annotated with ANNOVAR (v20210201; <https://annovar.openbioinformatics.org/>).

Molecular analysis was performed using NGS and revealed a c.1231G>T (p.Val411Leu) mutation (variant allelic frequency was 45.23%) in exon 13 of the POLE gene (Fig. 9). The TP53 gene harbored three mutations: c.809T>G (p.Phe270Cys) in exon 8, c.637C>T (p.Arg213Ter) in exon 5 and c.413C>T (p.Alal38Val) in exon 6, with variant allelic frequencies of 17.63, 22.70 and 24.93%, respectively. The final pathological diagnosis was ECS with a POLE gene mutation, FIGO 2023 stage IA, POLE-mutant subtype (1).

Treatment and follow-up. After the surgery, the patient was referred to the Binjiang Branch of The Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) for consultation. After a comprehensive assessment, the doctors decided not to administer adjuvant therapy. The tumor was FIGO 2023 stage IA, POLE-mutant endometrial carcinosarcoma with less than one-half myometrial invasion and negative lymph nodes. POLE-mutant endometrial carcinoma is associated with an excellent prognosis, therefore, adjuvant therapy was withheld after multidisciplinary discussion, given the low risk of recurrence and the potential toxicities of adjuvant treatment. No recurrence or metastasis was observed during the 18-month follow-up period. The last follow-up was performed in September 2026.

Discussion

ECS, also known as malignant mixed Müllerian tumor, exhibits bidirectional differentiation and includes components of both epithelial carcinoma and mesenchymal sarcoma, displaying notable histological heterogeneity (1). It is a rare malignant tumor of the female reproductive system and accounts for ~5% of uterine malignancies among women with uterine cancer in Western populations (2). The incidence of ECS ranges from 2-5 cases per 100,000 women, and postmenopausal women (median age, 65 years) are at a greater risk. The 5-year overall survival rate is <40% (3), which is markedly lower than the survival rate of >80% typical of common endometrial cancer.

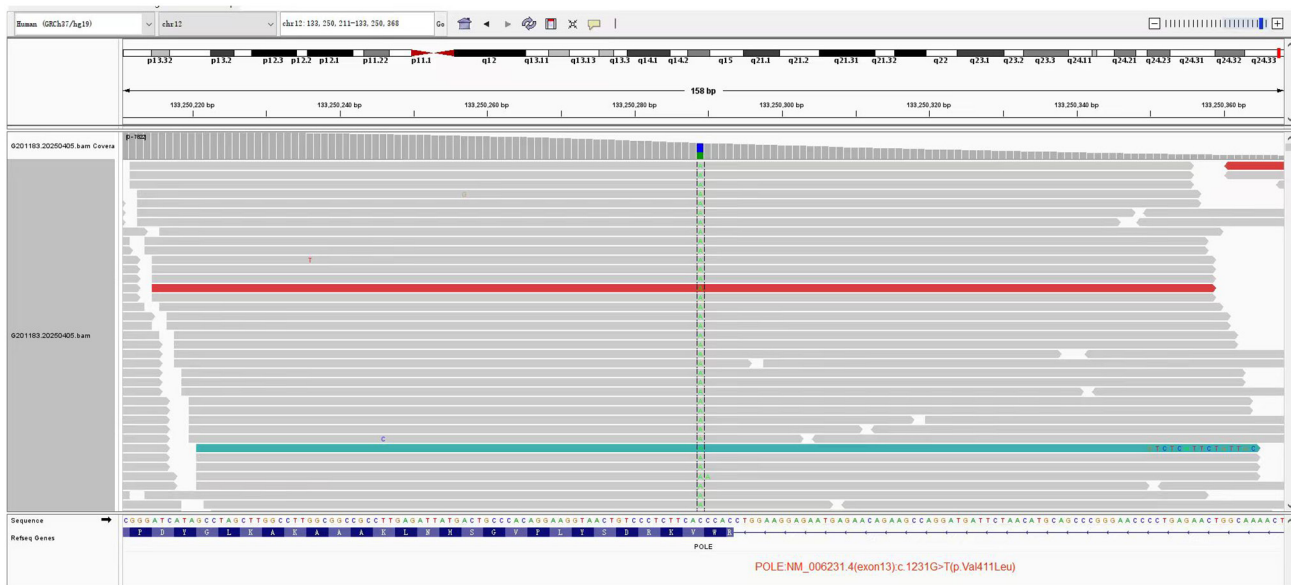


Figure 9. Molecular analysis showed a c.1231G>T (p.Val411Leu) mutation in exon 13 of the POLE gene (NM_006231.4) (the variant allelic frequency was 45.23%). POLE, DNA polymerase ϵ .

Moreover, the mortality rate of ECS is the highest among uterine malignant tumors. However, by applying molecular typing in endometrial cancer, some studies have revealed that the prognosis for patients with a POLE mutation is improved compared with the prognosis for those with a TP53-abnormal (9,10). Additionally, unnecessary pain and costs related to excessive treatment can be reduced. The present study presented a case of POLE-mutant ECS, and reviewed the relevant literature to provide novel insights into the diagnosis and treatment of these tumors within the endometrium.

ECS is composed of epithelial carcinoma (such as endometrioid carcinoma and serous carcinoma) and sarcomatous components, which are classified into homologous subtypes (including endometrial stromal sarcoma, leiomyosarcoma and undifferentiated sarcoma) or heterologous subtypes (including rhabdomyosarcoma, osteosarcoma and chondrosarcoma) (1). The cancer cells are irregularly arranged and characterized by large hyperchromatic nuclei and visible mitotic figures. Most sarcoma cells are spindle or polygonal, with notable atypia and active mitotic figures, and necrosis is common. Tumor cells often invade blood vessels, lymphatic vessels or surrounding tissues, and may undergo distant metastasis (for example, to the lung and liver) (2).

In a previous study, an immunohistochemical analysis demonstrated that the carcinomatous component expresses CK and epithelial membrane antigen, while the sarcomatous component expresses vimentin and other mesenchymal markers (CD10, smooth muscle actin, desmin and myogenin). Specific markers of heterologous components [such as MyoD1(+)/S-100(+)] have also been detected and TP53 is aberrantly expressed in ~50% of cases (abnormal type) (2). In the present study, histological examination of tissue samples from the patient revealed that they had high-grade endometrioid carcinoma, mucinous adenocarcinoma and undifferentiated sarcoma. Immunohistochemical staining revealed the carcinoma component had positive expression of epithelial markers and the sarcomatous component had vimentin positivity. TP53

showed aberrant immunohistochemical overexpression. The microsatellite stability marker was not lost, as demonstrated by intact expression of MMR proteins on immunohistochemistry. Based on these findings, a pathological diagnosis of ECS was confirmed (TP53-abnormal type).

A previous study revealed that POLE-mutant endometrial cancer generally exhibits microsatellite stability (65%) and TP53 gene mutations in ~35% of cases (7). In the absence of molecular typing, POLE-mutant endometrial cancer with good prognosis may be misdiagnosed and treated as invasive endometrial cancer, which has an unfavorable prognosis; this may lead to unnecessary overtreatment and thus harm the patient. The development of molecular subtyping and its application in endometrial cancer led the 2020 5th edition of the WHO classification of tumors of the female reproductive system to recommend using a modified version of The Cancer Genome Atlas (TCGA) classification. The classification scheme also proposed a diagnostic algorithm based on sequencing of the POLE gene, mismatch repair (MMR) protein immunohistochemistry and TP53 immunohistochemistry. Subtyping follows a hierarchical algorithm in sequence: POLE-mutant, MMR-deficient (MMRd), non-specific molecular profile (NSMP) and TP53-abnormal subtypes (1). Endometrial carcinomas harboring both pathogenic *POLE* exonuclease domain mutations and *TP53* aberrations are classified as the POLE-mutant subtype (1). Researchers have also performed molecular subtyping of endometrial cancer via biopsy before surgery; this strategy provides early prognostic value for guiding personalized treatment (12). Endometrial cancer after surgery, including carcinosarcoma, is also suitable for the modified TCGA classification (1).

In the current patient, TP53 showed aberrant immunohistochemical overexpression and the MMR proteins MLH1, MSH2, MSH6 and PMS2 were positively expressed, as determined by immunohistochemistry. NGS confirmed the presence of the c.1231G>T (p.Val411Leu) mutation in exon 13 of the POLE gene and three distinct *TP53* mutations, which

agreed with the diagnosis of ECS with POLE mutation. Based on the findings, the original stage IIc was updated to stage I Am-POLE mut (FIGO 2023) (13).

As reported in previous studies, POLE mutations occur in 7-12% of endometrioid carcinoma cases (4,5) and 2.7% of ECS cases (10). Nero *et al* (14) reported that of 61 (61/596; 10.2%) patients with endometrial carcinoma with POLE hotspot mutations, 27 (44.3%) and 34 (55.7%) patients had low- and high-grade cancer, respectively; 20 (32.8%) patients had LVSI; and 16 patients had co-mutations [MMRd, 9, 56.3%; TP53-abnormal, 4, 25.0%; MMRd plus TP53-abnormal, 3, 18.8%]. Furthermore, FIGO 2023 staging revealed that 57 cases (93.4%) were stage IA with POLE-mutant subtype, and four cases (6.6%) were stage III-IV. The median tumor mutation burden (TMB) was 150.8 mut/Mb (14). Notably, in endometrial carcinoma (including ECS), pathogenic *POLE* exonuclease-domain mutations mainly occur in six exons (exons 9-14), and the mismatch base cannot be recognized and repaired; this leads to an abnormal increase in the number of genomic mutations and causes tumorigenesis (4). This site is located in the exonuclease domain, and endometrial carcinoma carrying mutations in the exonuclease domain of *POLE* usually has a TMB exceeding 100 mut/Mb (15). In the context of a combined TP53 mutation (which ordinarily confers the poor prognostic characteristic of the TP53-abnormal subtype), the *POLE* mutation may still dominate the biological behavior. Nero *et al* (14) and Bogani *et al* (16) reported that four and 20 patients with endometrial cancer (25.0 and 27.8%, respectively) with both *POLE* and TP53 mutations had a better prognosis than patients with TP53-abnormal subtype lacking *POLE* mutations (14,16). Therefore, the present case was consistent with the WHO classification of *POLE* mutation.

For prognosis and treatment, comprehensive staging surgery is conducted in the early stages, while cytoreductive surgery is performed in later stages. Surgical pathological staging and adjuvant therapy, including systemic therapy and radiotherapy, are based on postoperative pathology. Patients for whom resection will not be satisfactory may be reassessed for surgery following chemotherapy or radiotherapy (17). While *POLE*-mutant ECS has demonstrated favorable outcomes in limited clinical series (8-10), substantial long-term prognostic data are preliminary and continuously evolving. As this subtype is rare [accounting for 2.7% of all ECS cases (10)] and single-case reports have limitations (for example, small overall sample size, absence of TMB data and individual variability in biological behavior), there is a risk of overgeneralization of prognostic conclusions from isolated cases. Further validation is required through larger-scale cohorts with extended follow-up to confirm the durability of favorable outcomes and to determine the effect of concurrent genetic alterations (for example, TP53 mutations) on long-term prognosis. Molecular typing should be performed to guide future treatment decisions. If stage I and II patients have *POLE* mutations, they can be closely followed up and observed regularly with full communication without radiotherapy and chemotherapy (8,18). Hammer *et al* (9) reported on 11 patients with *POLE*-mutant ECS, with mean and median follow-up times of 24.3 and 14.1 months, respectively (range, 1.4-61.1 months); no disease recurrence or death was detected in 10 patients, whereas one patient with a subclonal *POLE* mutation died 1.4 months after

surgery. Toboni *et al* (10) reported that the median overall survival of 48 patients was 74.8 months, which was notably longer than that of other subtypes. Bhangoo *et al* (11) reported a case of a stage III chemotherapy-ineffective relapse patient who was found to have a *POLE* mutation by molecular detection; the condition improved after 12 months of follow-up after immunotherapy; however, as this is a case report, more data are needed to confirm these findings.

In terms of advantages, the present case of *POLE*-mutant ECS is rare and has a unique pathological component of mucinous adenocarcinoma. After a comprehensive analysis, further treatment was not required, which increases the reference value of clinical diagnosis and treatment of ECS with *POLE* mutations. In terms of limitations of the present study, only a single case report was provided with a short follow-up period (18 months) and no TMB data, which restricts the generalizability of the prognostic observations. Therefore, long-term follow-up of this patient and data on more clinical cases are necessary to validate the prognostic significance of *POLE* mutations in ECS.

In summary, the present diagnosis and treatment experience combined with the literature review suggests that *POLE* mutations are rare in ECS and may be associated with a relatively favorable short-term prognosis; however, long-term outcomes need to be confirmed in larger-scale studies. For morphologically high-grade ECS, molecular subtyping should be routinely performed, particularly to determine the status of *POLE* mutations. When a *POLE*-mutant subtype is diagnosed, adjuvant therapy can be administered individually based on a comprehensive evaluation of tumor stage to reduce the risk of overtreatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be found in the Genome Sequence Archive for Humans under accession number HRA014729 or at the following URL: <https://ngdc.cncb.ac.cn/gsa-human/browse/HRA014729>.

Authors' contributions

YZ was responsible for the conceptual framework design and initial manuscript drafting of this case report. HG participated in the conceptual design, methodological design, data collation, formal analysis and implementation of the study. BH was responsible for project management, result validation, initial manuscript writing, and manuscript revision and review. BH and YZ confirm the authenticity of all the raw data. BH and YZ confirm the accuracy and integrity of all raw clinical data of this study and are responsible for the validity of the original data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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