

CASE REPORT

A case of ruptured epithelioid uterine leiomyosarcoma

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Abstract

Background: We report a rare case of epithelioid uterine leiomyosarcoma presenting with tumor rupture, a rare complication of uterine sarcomas. **Case:** The patient was a 47-year-old woman who was receiving filgotinib for ulcerative colitis and presented with genital bleeding. A uterine mass was detected, and malignancy was suspected. During the workup, she developed fever, genital bleeding, and lower abdominal pain and re-visited the emergency department. Coronavirus disease and intrauterine infections were suspected, and she was hospitalized. Despite antibiotic administration, no clinical improvement was observed. Computed tomography revealed irregular margins between the tumor and uterine muscle layer on the uterine fundus, raising strong suspicion of malignant tumor rupture. She was transferred to a tertiary care center and underwent total hysterectomy. Intraoperatively, the rupture site was covered by the omentum, and intra-abdominal spread of inflammation was limited. Histopathological examination revealed coagulative necrosis, proliferation of tumor cells with round nuclei, and numerous mitotic figures, leading to a diagnosis of epithelioid uterine leiomyosarcoma. Local recurrence at the vaginal stump was observed 10 months postoperatively, and treatment is ongoing. **Conclusions:** In this case, the diagnosis was triggered by genital bleeding. During evaluation, tumor rupture occurred, but clinical symptoms were minimal due to coverage of the rupture site by the omentum, making diagnosis challenging. Thorough screening for malignancy and careful monitoring are essential when using Janus kinase inhibitors.

Keywords

Epithelioid uterine leiomyosarcoma; Rupture; Filgotinib; COVID-19

1. Introduction

Uterine leiomyosarcoma (uLMS) is a rare malignant tumor, accounting for approximately 1–2% of all uterine malignancies, and most commonly occurs in postmenopausal women [1, 2]. It is known for its high malignancy, with a tendency for early hematogenous spread and distant metastasis to other organs, resulting in a poor prognosis [1, 2]. Tumor rupture in uterine sarcomas is extremely rare, with only a few recent cases reported in the literature [3]. Among the subtypes of uLMS, the epithelioid variant is particularly rare and poses diagnostic challenges, often requiring immunohistochemical and molecular evaluation to distinguish it from other mesenchymal tumors [4].

Here, we report an extremely rare case of epithelioid uLMS in a patient receiving filgotinib for ulcerative colitis, which was initially suspected following genital bleeding and subsequently ruptured during hospitalization for coronavirus disease (COVID-19) infection. To the best of our knowledge, this is the first reported case of ruptured epithelioid uLMS occurring under Janus kinase (JAK) inhibitor therapy, highlighting the

need for careful malignancy screening and close interdisciplinary follow-up in immunosuppressed patients.

2. Case

The patient was a 47-year-old nulligravid, nulliparous woman with a body habitus consistent with obesity. She had a history of appendectomy and ulcerative colitis, for which she was being treated with filgotinib at our hospital's gastroenterology department. No other relevant medical, surgical, or family histories were reported. An abdominal computed tomography (CT) scan performed for evaluating ulcerative colitis lesions revealed a uterine mass measuring 110 × 80 mm with a tendency to enlarge. Due to the presence of abnormal genital bleeding, she was referred to our department for further evaluation. On speculum examination, a hemorrhagic mass was observed in the vagina, and a cytological smear and tissue biopsy were obtained from the tumor.

Three days after the initial visit, she presented to the emergency department with a high fever of approximately 39 °C, lower abdominal pain, and genital bleeding. The abdominal

examination revealed no tenderness or signs of peritoneal irritation, and no respiratory symptoms were noted. However, she tested positive for the severe acute respiratory syndrome coronavirus (SARS-CoV-2) antigen. Suspecting COVID-19 and intrauterine infections, she was admitted for further evaluation and treatment.

At the time of admission, the speculum examination showed a tumor originating from the uterus extending caudally and protruding into the vagina through the external cervical os, appearing as a hemorrhagic mass measuring approximately 50 × 30 mm. On bimanual examination, the uterus had poor mobility. Transvaginal ultrasonography revealed a heterogeneous mass with irregular margins measuring 100 × 89 mm in the uterine body.

Laboratory test results indicated anemia with a hemoglobin level of 8.9 (reference range: 11.5–15.0) g/dL, mean corpuscular volume of 82 (reference range: 80–100) fL, elevated C-reactive protein (CRP) level of 12.6 (reference range: <0.3) mg/dL, and mildly elevated lactate dehydrogenase level of 294 (reference range: 124–222) U/L. Levels of tumor markers (cancer antigen 125, carbohydrate antigen 19-9, and carcinoembryonic antigen) were within normal limits.

Contrast-enhanced chest and abdominal CT performed at admission (Fig. 1a) revealed a mass measuring 110 × 80 mm centered on the anterior uterine wall, containing high-density areas suggestive of hemorrhage. Part of the tumor protruded into the vagina, with increased density in the surrounding adipose tissue, but no definitive signs of tumor rupture were observed. No lymph node metastasis, peritoneal dissemination, or distant metastasis was detected, and both ovaries appeared normal.

Pelvic magnetic resonance imaging (Fig. 1b) showed the tumor centered on the anterior uterine wall, extending downward to the cervical canal. On T2-weighted images, the tumor exhibited intermediate signal intensity, and diffusion-weighted imaging showed high signal intensity with heterogeneous areas suggestive of hemorrhage and necrosis.

The cytological smear obtained from the tumor protruding into the cervical canal at the initial visit (Fig. 2a) showed cells with high nuclear-to-cytoplasmic ratios against a necrotic background, possessing round to spindle-shaped nuclei with coarse chromatin, leading to a diagnosis of suspicious positive cytology.

Tissue biopsy from the tumor (Fig. 2b) revealed numerous necrotic areas and scattered, enlarged, and short spindle-shaped and giant cells. Immunohistochemical staining showed desmin-negative, estrogen receptor (ER)-negative, and Common Acute Lymphoblastic Leukemia Antigen (CD10)-positive results and a Ki-67 labeling index of <1%. Despite testing positive for the SARS-CoV-2 antigen, the patient did not develop respiratory symptoms during hospitalization and was managed conservatively. Suspecting intrauterine infection, vaginal discharge and blood cultures were obtained, and intravenous administration of tazobactam/piperacillin (4.5 g every 8 hours) was initiated. Filgotinib was discontinued due to concerns of worsening infection. However, the fever persisted with fluctuations between 38 °C and 39 °C, and CRP levels remained elevated without improvement. Although no peritoneal irritation signs were observed, the patient re-

ported intermittent lower abdominal pain with a numeric rating scale score of approximately 3, which was alleviated by oral acetaminophen (500 mg). Vaginal and blood cultures were negative.

On the ninth day of hospitalization, a repeat contrast-enhanced CT scan (Fig. 3) was performed to investigate the source of infection. The image showed disruption of the contour between the mass and the uterine myometrium on the cranial side of the mass, with overlying tissue presumed to be the omentum. Fluid accumulation and free air were observed within this area, strongly suggesting rupture of the uterine mass. Considering the need for perioperative management at a higher-level medical facility, the patient was emergently transferred and underwent emergency surgery on the same day.

Intraoperative findings revealed a ruptured tumor at the uterine fundus, with the rupture site covered by the omentum, preventing exposure of the tumor to the peritoneal cavity. Both adnexa appeared normal macroscopically. A small amount of ascites was present, but no evidence of peritoneal dissemination was found. Based on these findings, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy were performed via laparotomy. Pathological examination (Fig. 4) showed a yellowish-white tumor measuring approximately 80 mm extending from the uterine body to the fundus, with internal hemorrhage and necrosis. A clear perforation was observed on the anterior wall. Histopathological examination of the resected specimen revealed two distinct tumor components: an area composed of cells with round nuclei, prominent nucleoli, and eosinophilic cytoplasm exhibiting 34 mitoses per 10 high-power fields (Fig. 5) and an area with proliferating spindle-shaped tumor cells (Fig. 6). Immunohistochemical staining showed that the area in Fig. 5 was negative for α -smooth muscle actin (α -SMA) and desmin; partially positive for caldesmon; positive for CD10; negative for Cluster of Differentiation 117 (CD117), Estrogen receptor (ER), Progesterone Receptor (PgR), cyclin D1, *BCL6* Corepressor (BCOR), and Anti-Epithelial Antigen 1/3 (AE1/3); and partially positive for Epithelial Membrane Antigen (EMA), with a Ki-67 labeling index of 20%. The area in Fig. 6 was positive for α -SMA, desmin, and caldesmon; negative for CD10; and shared the same staining pattern as area A for other markers, with a Ki-67 labeling index of 5%. These findings indicated different immunohistochemical patterns in areas 5 and 6. Although the tumor exceeded 50 mm in size, it did not invade into both adnexa or the omentum, and the ascitic cytology result was negative. Based on these findings, the tumor was diagnosed in March 2024 as a ruptured epithelioid leiomyosarcoma of the uterus, staged as pT1bNXM0, indicating pathological tumor stage 1b, regional lymph nodes cannot be assessed, and no distant metastasis, corresponding to International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB.

The patient recovered without postoperative complications and was discharged on postoperative day 10 in stable condition. Due to the presence of tumor rupture, the patient was considered at high risk for recurrence and underwent six cycles of adjuvant chemotherapy with doxorubicin and cisplatin.

However, contrast-enhanced CT performed after the

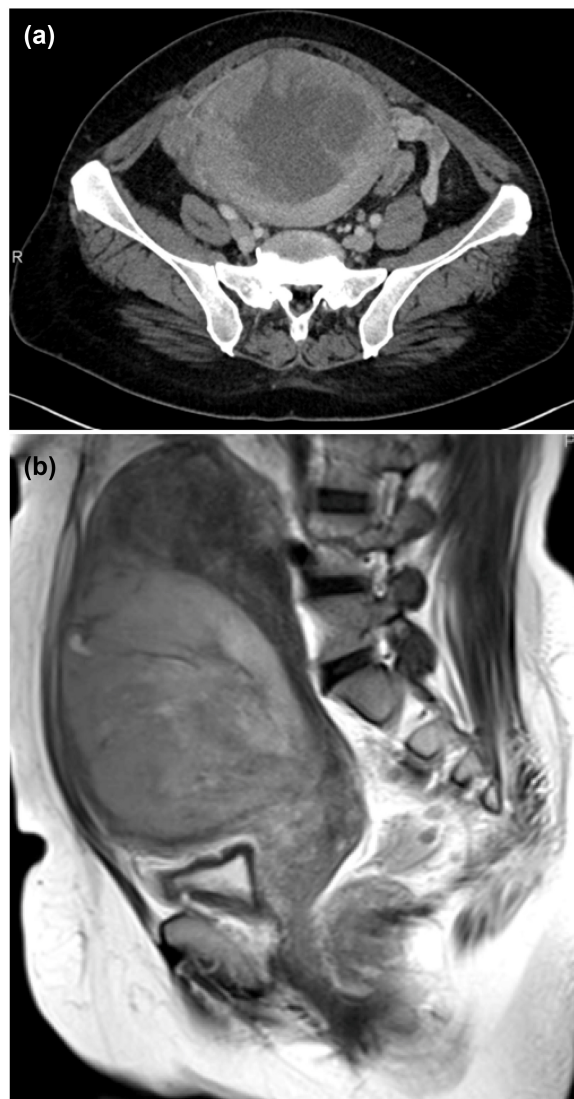


FIGURE 1. Preoperative imaging studies. (a) Contrast-enhanced computed tomography images (on admission). The mass centered on the anterior uterine wall contains high-density areas suggestive of hemorrhage and is associated with increased attenuation in the surrounding adipose tissue. However, no definitive findings indicate tumor rupture. (b) T2-weighted magnetic resonance imaging. A 110-mm mass centered on the anterior uterine wall exhibits intermediate signal intensity and extends downward in a drooping manner, reaching the endocervical canal.

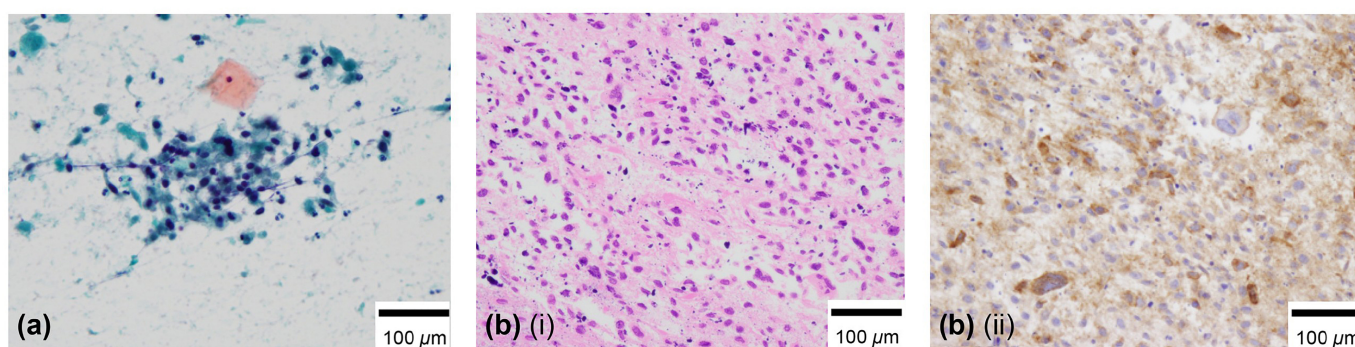


FIGURE 2. Diagnostic cytology and histopathology. (a) Cytological smear (Papanicolaou staining). Degenerated cells with a high nuclear-to-cytoplasmic ratio are scattered, showing nuclear irregularity and increased chromatin levels. (b) Histological biopsy results. (i) Hematoxylin and eosin staining ($\times 400$): Degenerated cells with nuclear enlargement are observed. (ii) CD10 staining: Positive.

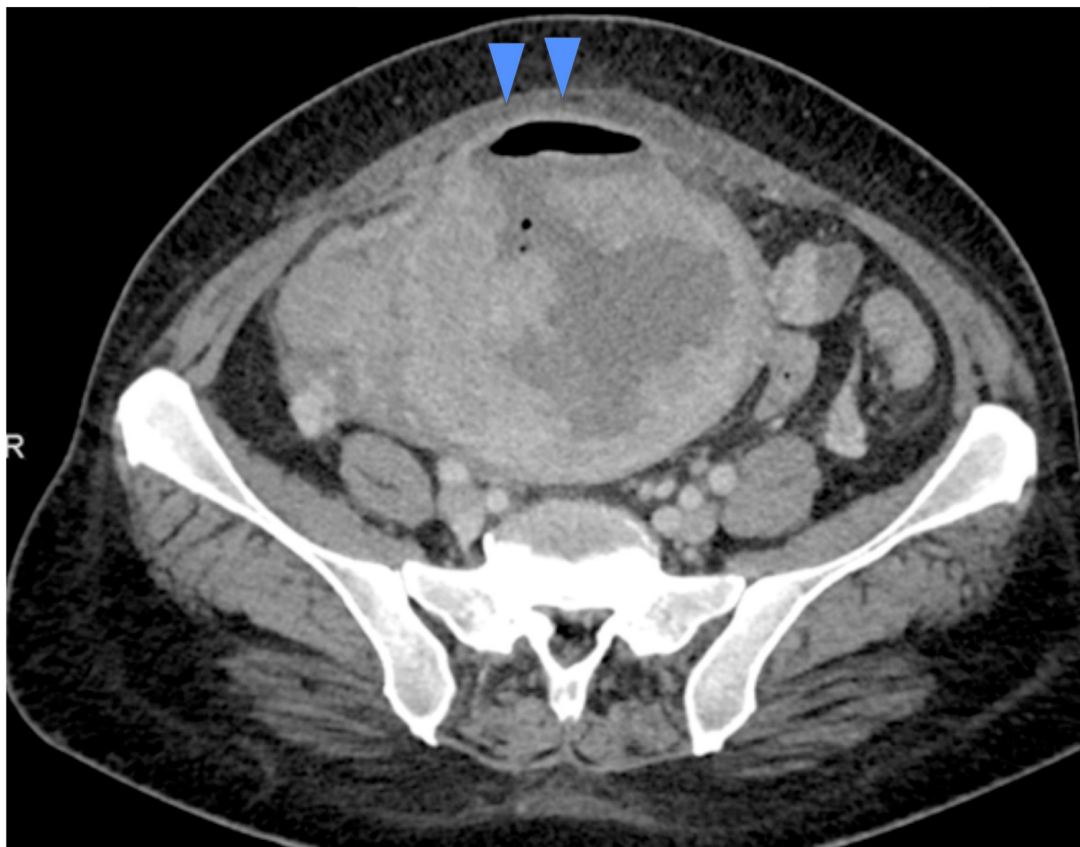


FIGURE 3. Contrast-enhanced computed tomography image (during hospitalization). Disruption of the contour between the tumor and the uterine myometrium is noted on the cranial side of the mass (blue arrowheads). The rupture site is covered with omental tissue, and fluid collection and free air are observed.

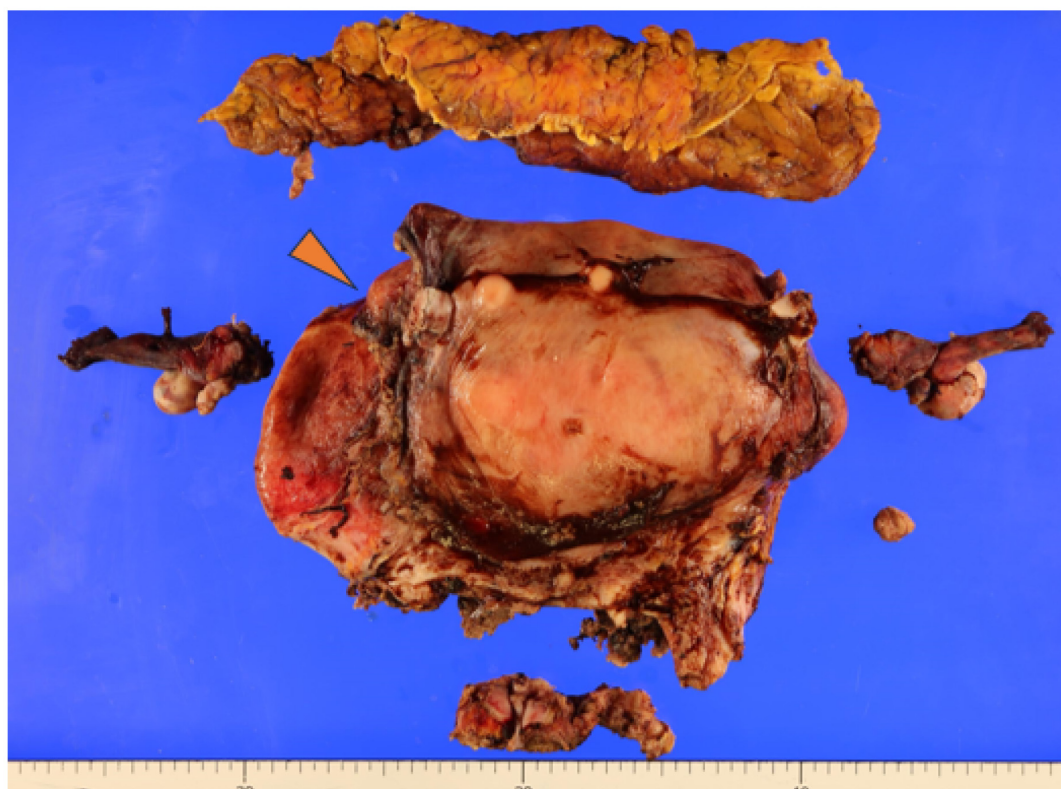


FIGURE 4. Macroscopic findings. A yellowish-white tumor measuring approximately 80 mm extends from the uterine body to the fundus, with areas of hemorrhage and necrosis. A clear perforation is noted in the anterior uterine wall.

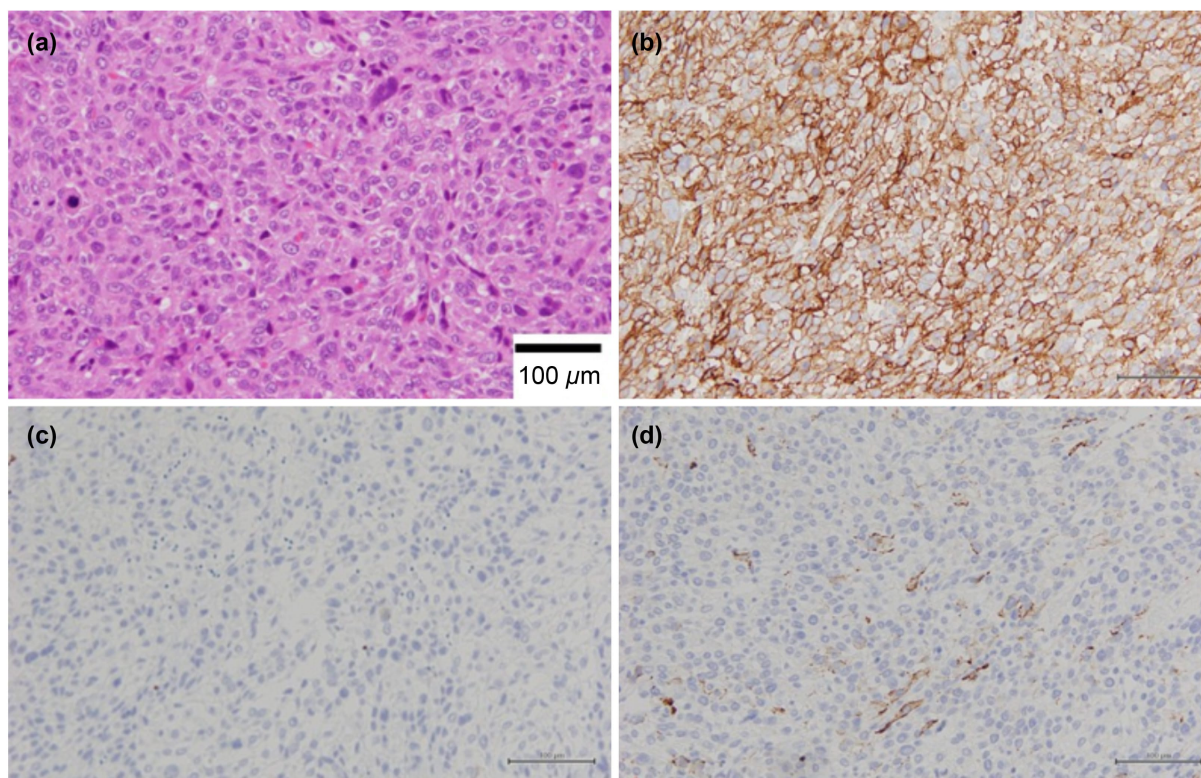


FIGURE 5. Histology of the epithelioid leiomyosarcoma component. (a) Hematoxylin and eosin (H&E) staining ($\times 400$): Solid proliferation of tumor cells with round and prominent nucleoli and mitotic figures are observed. (b) CD10 staining: Positive. (c) Desmin staining: Negative. (d) Caldesmon staining: Focally positive.

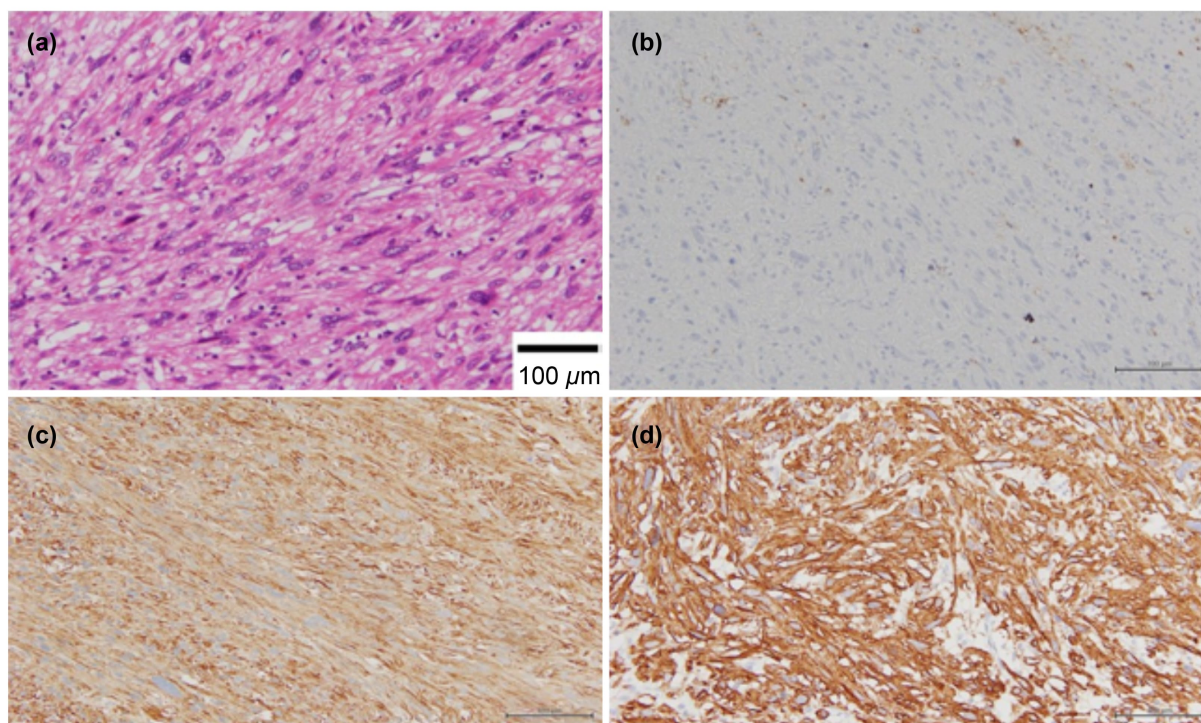


FIGURE 6. Histology of the spindle cell leiomyosarcoma component. (a) H&E staining ($\times 400$): Proliferation of spindle-shaped tumor cells showing nuclear pleomorphism and irregularity. (b) CD10 staining: Negative. (c) Desmin staining: Positive. (d) Caldesmon staining: Positive.

chemotherapy cycles revealed recurrence at the vaginal stump, indicating a partial response to the initial regimen. The patient is currently undergoing combination therapy with docetaxel and gemcitabine. Local recurrence at the vaginal stump was confirmed 10 months postoperatively.

Regarding the comorbid ulcerative colitis, remission was initially induced with budesonide tablets, followed by maintenance therapy with vedolizumab (300 mg), resulting in a stable course without relapse.

3. Discussion

uLMS is the most common type of uterine sarcoma, accounting for approximately half of all cases, with 250–300 cases reported annually in Japan. uLMS is histologically classified into three subtypes: spindle cell, myxoid, and epithelioid. Among these, the epithelioid subtype is extremely rare, with only five cases reported in a previous study [5]. Epithelioid uLMS differs histopathologically from the conventional spindle-cell type, making diagnosis difficult in some cases. The mechanisms by which smooth muscle-derived tumors acquire epithelioid morphology remain unclear. Epithelioid morphology is defined by polygonal tumor cells with eosinophilic cytoplasm and round-to-oval nuclei, ranging from purely epithelioid to mixed types with <50% spindle-cell components [6]. According to the fifth edition of the World Health Classification of Female Genital Tumors, a diagnosis of epithelioid leiomyosarcoma is recommended when at least one of the following criteria is met: (1) moderate to severe cytologic atypia, (2) tumor cell necrosis, or (3) ≥ 1.6 mitoses per mm^2 [7]. In the present case, the tumor exhibited substantial atypia, 34 mitoses per 10 high-power fields, and coagulative necrosis, thus meeting all the diagnostic criteria. These histological findings are consistent with those of a large institutional study by Chapel DB *et al.* [6], in which 81 out of 1177 uLMSs (7%) were classified as epithelioid. This previous study highlighted key aggressive features including infiltrative tumor borders (89%), necrosis (80%), vascular invasion (47%), and high mitotic activity (median 26 mitoses per 2.4 mm^2). Immunohistochemically, positivity for α -SMA, desmin, and caldesmon was commonly observed, while hormone-receptor expression was variable—findings that were mirrored in our case. In tumors with epithelioid morphology, distinguishing leiomyosarcoma from perivascular epithelioid cell tumor (PEComa) is critical. The desmin-negative, CD10-positive, and ER-negative immunoprofile seen in this case initially raised suspicion for a non-smooth muscle mesenchymal malignancy. However, the resected specimen exhibited the same immunoprofile in its epithelioid component, suggesting that the biopsy sample was collected from that area. Recent molecular pathology studies have further complicated this differential diagnosis. Katsakhyan *et al.* [8] reported cases of uLMS with co-existing PEComa components, which shared identical genetic alterations, such as tumor protein p53 (*TP53*) mutation, retinoblastoma 1 (*RBI*) and alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) loss, and fumarate hydratase (*FH*) deficiency, indicating a clonal relationship. These findings support the hypothesis that a subset of uterine PEComas may arise through differentiation or

dedifferentiation from smooth muscle progenitor cells within uLMS.

Rupture of uLMS is rare, and spontaneous rupture is particularly uncommon [9, 10]. In this case, the rupture site was within the epithelioid component, which showed a high Ki-67 index of 20%, suggesting that rapid tumor growth may have caused the rupture. While necrosis, bleeding, and rupture are well-documented features of uterine sarcomas [11], their co-occurrence during treatment with a JAK inhibitor—filgotinib—renders this case clinically unique. Although no previous reports have established a causal relationship between filgotinib and tumor rupture, this rare constellation of events during immunomodulatory therapy warrants further attention. Additionally, this case occurred during treatment with filgotinib for ulcerative colitis and was complicated by COVID-19 infection and tumor rupture. JAK inhibitors are associated with an increased risk of infections due to their immunosuppressive properties [12, 13]. Although the direct oncological effects of filgotinib remain unclear, its immunosuppressive action may have contributed to the atypical clinical presentation, including persistent fever and possible intrauterine infection. This highlights the importance of thorough malignancy screening and interdisciplinary follow-up when initiating immunosuppressive therapy, especially in patients with potential underlying neoplastic conditions. Epithelioid uLMS is considered to have a poorer prognosis than the conventional type, with shorter median survival and lower 5-year survival rates [6]. In this case, local recurrence at the vaginal stump was observed 10 months postoperatively, and chemotherapy is ongoing. Careful monitoring for peritoneal dissemination is necessary.

This case occurred during treatment with filgotinib for ulcerative colitis and was complicated by COVID-19 infection and tumor rupture. JAK inhibitors increase infection risk and should be used cautiously in immunocompromised patients [14]. Nevertheless, baricitinib reduces COVID-19 mortality [15], and ruxolitinib suppresses cytokine storms [16], showing variable effects among JAK inhibitors. Although the role of filgotinib in tumor rupture is unclear, the absence of respiratory deterioration enabled timely surgery with a favorable outcome. Notably, a CT scan before filgotinib initiation suggested uterine leiomyoma. Tofacitinib has been linked to increased risk of lung cancer, lymphoma, and skin cancer [17], and JAK2 inactivation promotes endometrial cancer progression [18]. Thus, careful malignancy screening is essential before JAK inhibitor use. Conversely, inhibition of the JAK-signal transducer and activator of transcription (STAT) pathway may suppress tumor progression, and its application to gynecologic cancers is under investigation [19, 20]. Although there is no established evidence linking filgotinib to tumor rupture and a direct drug interaction remains unclear, immunosuppression may have played a contributory role. Careful screening for neoplastic lesions and interdisciplinary follow-up are warranted when using JAK inhibitors, as highlighted by this case. From a clinical perspective, this case emphasizes the importance of careful histopathological diagnosis of epithelioid uLMS, vigilance for atypical presentations in immunosuppressed patients, and the need for malignancy screening when initiating JAK inhibitors. It further highlights the value of multidisciplinary management in achieving timely diagnosis and intervention in

rare gynecologic malignancies.

However, some limitations should be considered. This report describes a single case, which restricts the ability to draw conclusions regarding causality between filgotinib, COVID-19, and tumor rupture. Additionally, no molecular genetic analysis was performed, limiting insights into tumor biology. Finally, the rarity of epithelioid uLMS restricts generalizability, and further case accumulation is necessary.

4. Conclusions

We reported an extremely rare case of ruptured epithelioid uLMS in a patient receiving filgotinib for ulcerative colitis during COVID-19 infection. Although necrosis, bleeding, and rupture are known features of uterine sarcomas, their occurrence under JAK inhibitor therapy highlights the need for careful malignancy screening and close interdisciplinary follow-up in immunosuppressed patients. While no direct link between filgotinib and tumor rupture can be established, this case underscores the need for further investigation into the interaction between immunosuppressive therapy and rare gynecologic malignancies.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTIONS

NK—Conceptualization; Writing—original draft; Clinical management of the patient. SF—Conceptualization; Literature review; Writing—review & editing. KY, YY—Data collection; Writing—review & editing. AK—Imaging analysis; Writing—review & editing; Visualization. CO—Pathological analysis; Writing—review & editing; Visualization. HM—Clinical investigation; Writing—review & editing; Visualization. TS—Pathological diagnosis; Writing—review & editing; Visualization. SS, KF—Supervision; Writing—review & editing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was not required for this case report in accordance with the institutional policy. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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