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Imagination beyond imaging - when tuberculosis mimics endometrial cancer spread: a case report

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ABSTRACT

Background. In Europe, endometrial cancer ranks fourth among female neoplasms. Tuberculosis is one of the most common diseases affecting health globally. Moreover, tuberculosis is notorious for its ability to mimic other conditions, including cancer, especially when imaging results are misleading.

Case presentation. The present case involves a 72-year-old patient who presented to the gynaecological outpatient clinic with complaints of abnormal uterine bleeding. A diagnostic hysteroscopy led to the diagnosis of endometrial endometroid adenocarcinoma, moderately differentiated. Pre-operative staging using PET/TC scan revealed abnormal tracer accumulation in the lymph nodes along the right common iliac vessels, raising suspicion for metastasis. Based on this information, the patient was considered as an intermediate/high risk candidate for minimally invasive surgery, and underwent a total laparoscopic hysterectomy, together with bilateral salpingo-oophorectomy and bulky lymphadenectomy. Final histopathology revealed endometrioid adenocarcinoma of the uterine body, moderately differentiated (G2), hypermutated subtype, infiltrating beyond the internal half of the myometrium. Surprisingly, Mycobacterium tuberculosis complex was found in the lymph nodes. This finding completely changed the patient's follow-up and prognosis leading to brachytherapy and anti-tuberculosis 4-drug therapy.

Conclusions. The concurrency of endometrial carcinoma and tuberculosis (TB) is extremely rare, with only 9 cases reported in the living literature. However, clinicians must consider the possibility of their coexistence, especially in regions where tuberculosis is endemic and in the context of endometrial malignancy with abdominopelvic lymphadenopathy. Close collaboration among multidisciplinary teams is essential to achieve optimal outcomes in such challenging and rare cases.

INTRODUCTION

Endometrial cancer (EC) is the seventh most common cancer globally, predominantly affecting individuals aged 65 to 75. In Europe, uterine cancer is the fourth most frequent malignancy among women, with an incidence ranging from 12.9 to 20.2 per 100,000 individuals and a low mortality rate of 2.0 to 2.7 per 100,000 [1, 2]. This lower mortality is largely because 80% of EC cases are confined to the

uterus at diagnosis, often presenting as postmenopausal bleeding, facilitating early detection [1, 3]. Traditionally, ECs were classified into two subtypes based on their histopathological characteristics (type 1 and 2) [1]. However, this approach has been superseded by a more detailed classification system based on molecular phenotypes [2]. Currently, endometrial cancers are now classified into four categories: POLE ultra-mutated, microsatellite instability hypermutated, copy-number low, and copy-number high [4, 5]. POLE ultra-mutated ECs typically exhibit favourable outcomes, whereas p53-abn (copy number high) ECs tend to have the poorest clinical prognosis, irrespective of various factors such as risk group, adjuvant treatment, tumour type, or grade [6]. Lymphovascular space invasion (LVSI) is a critical predictor of lymph node metastasis and overall survival [7].

EC typically presents with abnormal uterine bleeding and vaginal discharge, with advanced cases exhibiting symptoms akin to advanced ovarian cancer [8]. Several non-genetic risk factors have been linked to an increased risk of endometrial cancer, particularly the endometrioid endometrial adenocarcinoma subtype. These risk factors include obesity, physical inactivity, excess exogenous estrogen, insulin resistance, and tamoxifen use after breast cancer [9].

The standard diagnostic workup for endometrial cancer comprised pelvic ultrasonography, office endometrial biopsy, or dilatation and curettage (D&C) with or without hysteroscopy. Imaging techniques like CT scan, MRI and PET/CT scan are used to assess metastasis. Staging and treatment plans are developed on a multidisciplinary basis, incorporating prognostic and predictive factors [8].

According to the latest European Society of Gynecological Oncology (ESGO) Guidelines (2021), patients with endometrial cancer can be stratified into five prognostic risk groups (**Table 1**), regardless of whether molecular classification is available or not [10].

As emphasized by the ESGO Guidelines [10], minimally invasive surgery is preferred even for high-risk patients. Standard surgery typically involves total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, excluding vaginal cuff resection (TLHBSO). However, infra-colic omentectomy staging should be performed in clinical stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated carcinoma. Omission of omentectomy may be omitted in clear cell and endometrioid carcinoma at stage I [10].

Regarding lymph node staging, sentinel lymph node biopsy could be an option for low-risk or intermediate-risk patients. It can also serve as an acceptable alternative to systematic lymphadenectomy for hi-

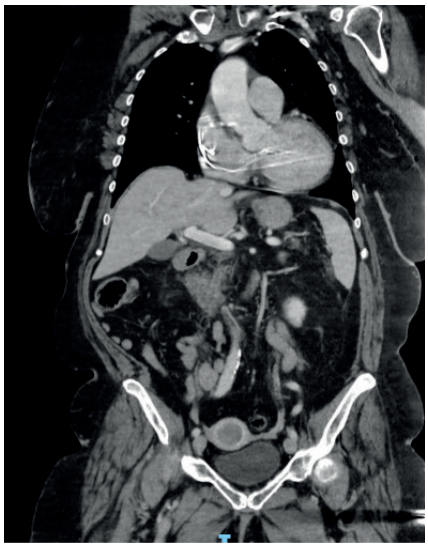
Table 1. *Definition of prognostic risk groups [8].*

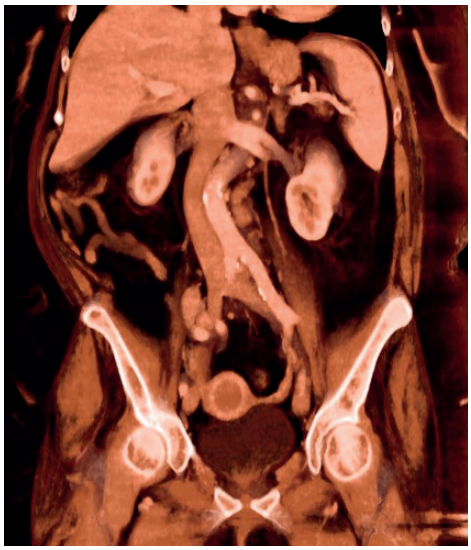
Risk group	Molecular classification unknown	Molecular classification known
Low	- Stage IA endometrioid + low-grade‡ + LVSI negative or focal	- Stage I–II POLEmut endometrial carcinoma, no residual disease - Stage IA MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal
Intermediate	- Stage IB endometrioid + low-grade‡ + LVSI negative or focal - Stage IA endometrioid + high-grade‡ + LVSI negative or focal - Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	- Stage IB MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal - Stage IA MMRd/NSMP endometrioid carcinoma + high-grade + LVSI negative or focal - Stage IA p53abn and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	- Stage I endometrioid + substantial LVSI regardless of grade a nd depth of invasion - Stage IB endometrioid high-grade‡ regardless of LVSI status - Stage II	- Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion - Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVSI status - Stage II MMRd/NSMP endometrioid carcinoma
High	- Stage III–IVA with no residual disease - Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	- Stage III–IVA MMRd/NSMP endometrioid carcinoma with no residual disease - Stage I–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease - Stage I–IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	- Stage III–IVA with residual disease - Stage IVB - Stage IVB of any molecular type	- Stage III–IVA with residual disease of any molecular type

gh-intermediate risk or high-risk diseases in stages I or II [10]. Further systematic pelvic lymph node dissection should be avoided if pelvic lymph node involvement is identified intra-operatively. Nevertheless, debulking of enlarged lymph nodes and para-aortic staging may be considered [10].
Fertility sparing treatment (FST) may be considered for patients with atypical hyperplasia (AH) or endometrial intraepithelial neoplasia (EIN), or for those with grade 1 endometrioid endometrial carcinoma without myometrial invasion and without genetic risk factors. In these cases, an endometrial biopsy, preferably via hysteroscopy, is essential [11, 12].
Patients must be informed that FST is not a standard treatment and is only appropriate for those with a strong desire to preserve fertility [11]
Adjuvant treatment recommendations for endometrial carcinoma are highly dependent on the prognostic group [10]. Patients with low-risk endometrial carcinoma typically do not require adjuvant therapy. Intermediate-risk patients may benefit from adjuvant brachytherapy to reduce vaginal recurrence, while those in the intermediate-high risk group without lymph node involvement might consider adjuvant brachytherapy or chemotherapy. External beam radiation therapy (EBRT) with concurrent and adjuvant chemotherapy or sequential chemotherapy and radiotherapy are recommended for high-risk diseases [10]. In stage III and IV endometrial carcinoma (including carcinosarcoma), surgical tumour debulking including enlarged lymph nodes should be considered if complete macroscopic resection is feasible and if the procedure is likely to maintain acceptable morbidity and quality of life. This decision should follow thorough preoperative staging and multidisciplinary discussion [10].
According to a recent World Health Organization (WHO) report, tuberculosis remains one of the most deadliest infectious diseases globally, responsible for approximately 1.5 million deaths in 2018 [13]. Tuberculosis and cancer are significant global health issues, with tuberculosis often mimicking other conditions and occasionally being misdiagnosed as cancer [14, 15]. Misdiagnoses can arise from false-positive PET/CT findings, oncological history, and elevated levels of carbohydrate antigens such as CA 125 of CA 19-9.
Abdominopelvic tuberculosis (APTB) is relatively rare, accounting for about 5% of all tuberculosis cases worldwide [16]. Clinical manifestations of APTB are typically non-specific, creating diagnostic challenges, especially when co-existing with pelvic malignancy. While endometrial cancer complicated by APTB is more common in regions with a high incidence of tuberculosis, the presented case describes an unusual instance of APTB in a patient without evident epidemiological risk factors for tuberculosis.

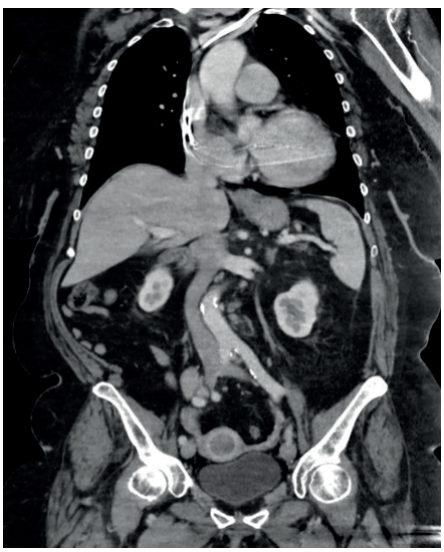
CASE PRESENTATION

A 72-year-old woman was referred to the gynaecological outpatient clinic due to abnormal uterine bleeding (AUB) during menopause. The patient is



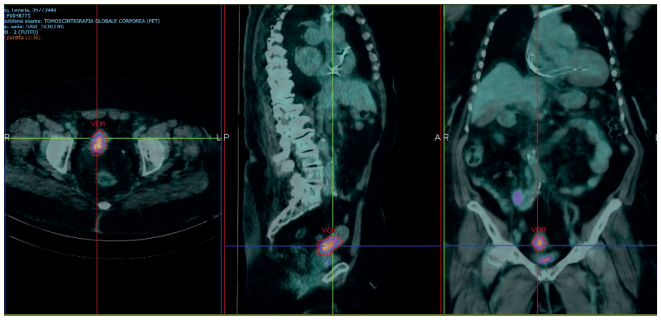


Figures 1, 2. *Abdominal CT scan: pathological lymph nodes along the right common iliac vessel.*

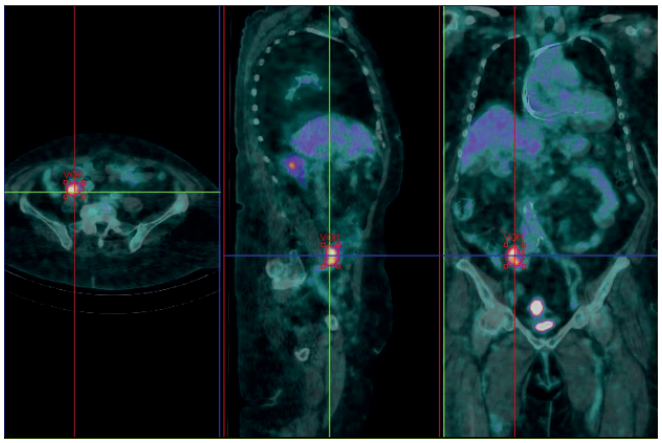


Figures 3. *Abdominal CT scan: para-aortic pathological lymph nodes.*

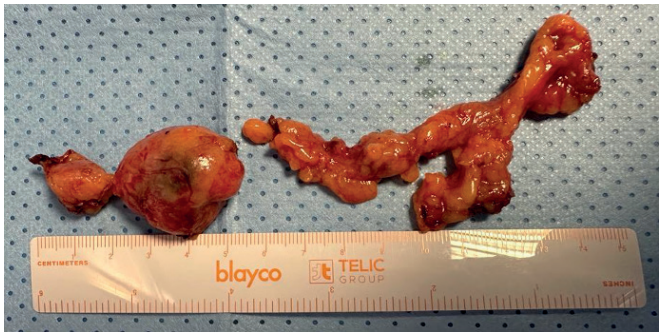
obese (body mass index 32) and nulliparous, with a medical history significant for arterial hypertension, chronic obstructive pulmonary disease and heart failure. Additionally, she has an implanted pacemaker and significant varicose veins in her lower limbs. There is no history of HIV, glucocorticoids use, diabetes, or other known immunosuppressing factors associated with an increased risk of contracting TB [17]. Furthermore, the patient did not report substance abuse, household contacts with infected individuals or recent travels to TB-endemic regions [18].
A transvaginal ultrasound revealed thickening of the endometrium (21mm), prompting a diagnostic hysteroscopy. During the procedure, a hypertrophic, whitish, and friable endometrium, suspicious for malignancy, was observed. Biopsies were performed, and histopathological examination revealed endometrial adenocarcinoma, endometrioid subtype, with villo-glandular, cribriform architecture, graded as low grade (G2).
Further staging investigations were conducted. A chest CT scan with contrast revealed calcific micronodules related to fibrotic-dysventilative outcomes and striae in the left lower lobe and in the lingular area. Additionally, apical pleural thickening on the right was noted, but no typical findings suggestive of tuberculosis such as upper lobe focal infiltration, cavitation, or fibrosis with traction or enlargement of hilar and mediastinal lymph nodes were observed [18].
An abdominal CT scan with contrast showed widening of the endometrial cavity, with a maximum thickness in sagittal reconstructions of approximately 23 mm. The endometrium exhibited non-homogeneous contrast-enhancement, consistent with the known endometrial cancer. Multiple enlarged lymph nodes were described in the iliac-obturator area, with the largest visible along the right common iliac vessels, measuring 28 × 18 × 37mm (**Figures 1** and **2**). Other lymph nodes were detected in the left para-aortic area, with a maximum measurement of 20 × 14 mm (**Figure 3**).
A PET/TC scan was performed to further investigate the suspicious lymph nodes. The scan revealed tracer accumulation in the endometrial cavity (**Figure 4**), as well as abnormal tracer accumulation along the iliac-obturator axis on the right, with the most significant accumulation along the common iliac vessels (**Figure 5**). These findings suggested metabolically active disease involvement.
After receiving cardiological and pneumological clearance, the patient underwent surgery. Accor-



Figures 4. *PET/TC scan: tracer accumulation in the endometrial cavity.*



Figures 5. *PET/TC scan: tracer accumulation along the iliac-obturator axis on the right, with the largest accumulation along the common iliac vessels.*



Figures 6. *Debulking of enlarged lymph nodes.*

ding to the ESGO guidelines [10], her disease was classified as an intermediate-high risk tumour (stage I, endometrioid subtype, lymphovascular space invasion), making her a candidate for minimally invasive surgery. An operative laparoscopy was performed, including total laparoscopic hysterectomy, bilateral salpingo-oophorectomy (TLHBSO), peritoneal washing, and debulking of enlarged lymph nodes (**Figure 6**). Systematic pelvic lymph node dissection was omitted, based on both the European Society of Gynecological Oncology Guidelines [10] and the patient's general conditions. Following the procedure, no macroscopical residual tumour was observed (TR: NED – no evidence of disease).

The definitive histological examination confirmed the diagnosis of moderately differentiated (G2), hypermutated subtype endometrioid adenocarcinoma of the uterine body, infiltrating beyond the internal half of the myometrium. Severe peritumoral acute and chronic inflammatory infiltration was noted, with no evidence of lympho-vascular neoplastic emboli. The uterine cervix and parameters were free from neoplasia. Following lymphadenectomy, the common iliac lymph nodes were negative for secondary disease but were positive for Mycobacterium tuberculosis complex.
Consequently, the final staging of disease was classified as pT1bNxMx, indicating an intermediate-risk endometrial carcinoma. After multidisciplinary discussion, the patient underwent brachytherapy. Given the coexistence of the M. tuberculosis complex infection, she also started a four-drug antituberculosis regimen (Isoniazid, Rifampin, Ethambutol, Pyrazinamide) [19]. Due to the interaction between Rifampicin and Rivaroxaban, the latter was replaced with Vitamin K Antagonist (VKA) anticoagulant therapy.
The patient tolerated the medications well, except for a single episode of cutaneous toxicity attributed to Rifampicin and Isoniazid. The diffuse macular erythema reported by the patient was managed with antihistaminic drugs, resulting in a temporary suspension of both medications. After three weeks, once symptoms completely resolved and upon dermatological recommendation, she resumed the four-drug regimen and is currently under close follow-up by both the gynaecologist and infectious disease specialist. She is now free from both oncological disease and tubercular infection.

DISCUSSION

The co-occurrence of endometrial carcinoma and tuberculosis is exceedingly rare, with only nine reported cases in the literature to our knowledge [20-25]. Tuberculosis (TB), due to its often subtle presentation, poses a significant diagnostic challenge [14]. The prevalence of TB infection (TBI) is higher among individuals born in or formerly residing in high incidence countries [26]. Italy, however, is not classified by the WHO as a high-burden country for TB [27]. Additionally, our patient had no clinical or epidemiological risk factor for TB, which is why routine screening tests such as tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) were not performed.
Endometrial cancer (EC) ranks as the fourth most common female cancer in Europe, posing a significant health burden in the Western World [1]. EC is staged surgically and examined pathologically, with key factors such as lesion grade, histological type and LVSI being recorded at all stages. The use of molecular classification testing (POLEmut, MMRd, NSMP, p53abn) enhances prognostic risk-group stratification and treatment decisions.
The 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system is widely used for EC (**Tables 2** and **3**) [28]. Surgical standard treatment involves a total hysterectomy with bilateral salpingo-oophorectomy and sentinel lymph node biopsy, while pelvic lymph node dissection and omentectomy are performed based on histological results. Although retrospective studies suggests that systematic lymphadenectomy may improve survival, randomized controlled trials have not shown significant benefits [29, 30]. To mitigate the risks associated with surgical procedures, alternative methods such as non-invasive imaging scans and sentinel lymph node biopsy [31, 32] are being increasingly considered.
PET/CT scanning is an alternative technique for staging endometrial cancer [33] due to its high positive predictive value (91.7%) [33]. However, PET/CT scans carry a risk of over-staging, because they may yield false-positive findings, particularly in infectious or inflammatory tissues [34, 35]. The case presented here is a remarkable example where the initial PET/CT scan suggested possible lymph node involvement, prompting an extensive lymphadenectomy. Contrary to the radiological findings, the histological examination of the lymph nodes revealed no metastases, significantly altering the patient's prognostic risk group.
A crucial concern in cases where TB is misdiagnosed as cancer is the potential transmission of TB to healthcare workers (HCW). Despite a general decrease in TB prevalence, HCWs remain at increased risk compared to general population [36]. Transmission occurs via inhalation of infected droplet nuclei, and procedures such as endotracheal intubation are among the most common ways these droplets can be dispersed [37].
Aligned with the WHO's "END strategy [38], initiated in 2015 and aiming to reduce TB incidence by 95% by 2030, prompt recognition and manage-

Table 2. *Cancer of the endometrium: 2023 FIGO staging [24].*

Stage	Description
I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium or non-aggressive histological type (ie, low-grade endometroid) with invasion of less than half of the myometrium with no or focal LVSI or good prognosis disease - IA1: non-aggressive histological type limited to an endometrial polyp or confined to the endometrium - IA2: non-aggressive histological types involving less than half of the myometrium with no or focal LVSI - IA3: low-grade endometroid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological typese limited to a polyp or confined to the endometrium
II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological typese with any myometrial involvement
III	Local and/or regional spread of the tumour of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis - IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) - IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB -	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum - IIIB1 Metastasis or direct spread to the vagina and/or the parametria - IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both - IIIIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis - IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Table 3. *2023 FIGO endometrial cancer stage with molecular classification [24].*

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAmPOLEmut	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICmp53abn	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

ment of TB are essential. This is crucial not only for the health of the patient but also for the safety of HCWs and the broader community.

The primary strengths of this study, given its nature, include raising awareness among readers, which may facilitate the detection of similar cases, particularly given its occurrence in a non-endemic area. However, the main limitations are inherent to the case report format, which precludes generalization. Moreover, it is generally more likely for PET-CT tracer accumulation to be associated with endometrial cancer rather than tuberculosis.

CONCLUSIONS

In summary, the co-occurrence of abdominal-pelvic tuberculosis alongside endometrial carcinoma represents a rare yet conceivable phenomenon, particularly in regions with high tuberculosis prevalence. Our case underscores the importance of considering tuberculosis in the context of endometrial malignancy, particularly with abdominopelvic tumour-free lymphadenopathy.
Misdiagnosing pelvic TB can lead to inadequate surgical interventions, compromising patients' quality of life and posing heightened contamination risks for healthcare workers. Conversely, under-staging endometrial carcinoma in patients with concurrent tuberculosis may underestimate the extent of tumoral disease, potentially facilitating dissemination and inadequate cancer management.
Given the challenges in pre-operative diagnostics to distinguishing APTB from endometrial carcinoma's lymph nodal metastasis, the authors propose intraoperative frozen section analysis for comprehensive surgical staging. While this approach may increase surgical morbidity, the potential ramifications of over-staging, misdiagnosis and subsequent mismanagement warrant careful consideration.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
M.G. Conceptualization, writing – original draft. F.S. and C.C. writing – review & editing. A.L. data curation, forma analysis. L.T. writing – review & editing. D.S. writing – review & editing. V.R. Conceptualization, writing – original draft.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
No ethical approval was required for this study.

Informed consent
Written informed consent was obtained by the patient.

Data sharing
Data are available under reasonable request to the corresponding author.

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