



Co-existent abdominoperitoneal tuberculosis with endometrial cancer: A diagnostic and surgical challenge

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ABSTRACT

The presence of abdominoperitoneal tuberculosis (APT) complicates the diagnosis, staging and management of endometrial cancer. Lymph node involvement in APT may mimic metastatic lymphadenopathy in patients with endometrial cancer. To our knowledge, there have only been 2 previous case reports on this topic. We will describe 3 cases of endometrial cancer co-existing with APT. The 1st case is a 57-year-old female who underwent elective total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLHBSO) and bilateral pelvic lymph node dissection (PLND). The final diagnosis is Stage 3C1 endometrial endometrioid carcinoma with mucinous differentiation. The 2nd case is a 70-year-old female who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) and PLND. The final diagnosis is a Stage 1A endometrioid adenocarcinoma. The 3rd case is a 63-year-old female who underwent TAHBSO and PLND and the final diagnosis was a mixed high-grade serous (90%) and endometrioid (10%) carcinoma of the endometrium. In these cases, the importance of surgical staging is emphasised to accurately stage endometrial cancer. Moreover, thorough peri-operative optimisations by a multi-disciplinary team are essential to improve the outcomes of surgery.

1. Introduction

Abdominoperitoneal tuberculosis (APT) is a relatively rare condition, accounting for about 5% of all tuberculosis (TB) cases worldwide (Sharma and Mohan, 2004). APTB may occur through the following pathways: (1) reactivation of latent TB infection, (2) ingestion of Mycobacteria in undercooked meat or unpasteurized milk products, or (3) haematogenous or lymphatic spread in the setting of active TB infection (also known as miliary TB) (Sharma and Mohan, 2004). The clinical manifestations of APTB tend to be non-specific, hence posing a diagnostic challenge especially in the setting of co-existing pelvic malignancy. These manifestations include abdominal pain, abdominal distension, fever, loss of weight, diarrhoea, and the presence of an abdominal mass (al-Quorain et al., 1993).

Endometrial cancer complicated by APTB may exist in areas of the world with higher incidence of tuberculosis. We present three cases of endometrial cancer with co-existing APTB. The 1st case was performed

laparoscopically while the rest were done with laparotomy. The diagnostic and management challenges are laid out in each case presentation.

2. Case presentation

2.1. Case 1

The first case is a 57-year-old para 2 female who presented with 1 year of post-menopausal bleeding, associated with severe back pain and fever for 1 month's duration. On examination, the abdomen was soft and non-tender with no masses felt. The cervix appeared normal.

Her pelvic ultrasound (US) scan revealed a 4.9 × 2.7 × 3.9 cm lesion with rich vascularity occupying the endometrial cavity. This patient underwent endometrial biopsy which revealed a FIGO Grade 2 endometrioid carcinoma.

Further staging scans were performed with computer tomography

Abbreviations: TLHBSO, Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy; PLND, Pelvic lymph node dissection; TB, Tuberculosis; TAHBSO, Total abdominal hysterectomy with bilateral salpingo-oophorectomy; US, Ultrasound; CT, Computer tomography; TAP, thorax, abdomen and pelvis; (MRI) pelvis, Magnetic resonance imaging; RHEZ, Rifampicin, isoniazid, ethambutol and pyrazinamide; PET, Positron emission tomography; PALND, Para-aortic lymph node dissection; PCR, Polymerase chain reaction.

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(CT) thorax, abdomen and pelvis (TAP) and magnetic resonance imaging (MRI) pelvis. Her CT TAP suggested an L3-L4 spondylodiscitis with adjacent large left psoas abscess, with findings suspicious for tuberculous aetiology (Fig. 1). A heterogeneous lesion was seen within the endometrial cavity confined to the uterus. Borderline retroperitoneal and pelvic nodes were indeterminate for metastasis or reactive changes from inflammation. There was no evidence of pulmonary metastasis or tuberculosis seen. A small amount of ascites and mild omental fat stranding were also noted.

Her MRI pelvis showed an enhancing endometrial mass involving the outer half of the myometrium suspicious for primary endometrial malignancy (Fig. 2). Areas of peritoneal nodularity and omental stranding were visualised, but they were of indeterminate aetiology.

The patient underwent radiologically-guided percutaneous drainage of the left psoas abscess for diagnosis and symptom control. The aspirates confirmed extrapulmonary TB. The patient was subsequently reviewed by the Infectious Diseases team, and started on TB treatment with rifampicin, isoniazid, ethambutol and pyrazinamide (RHEZ) for 2 months, followed by rifampicin and isoniazid for a further 9 months.

2 months after initiating TB treatment, this patient underwent elective total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLHBSO), bilateral pelvic lymph node dissection (PLND) and adhesiolysis. Intraoperatively, there were extensive miliary deposits seen over the entire abdominal cavity, small and large bowel, peritoneum and bladder. The small bowel, transverse colon and omentum were extensively adherent to the anterior abdominal wall. Frozen sections of the miliary deposits showed necrotizing granulomas.

Final histology of the pelvic lymph nodes showed separate involvement of metastatic carcinoma (2 lymph nodes) and granulomatous inflammation (1 lymph node). The patient had a stage 3C1 endometrial endometrioid carcinoma with mucinous differentiation. This patient recovered well post-operation and completed adjuvant chemotherapy (paclitaxel and carboplatin) with external pelvic radiotherapy. Currently, she remains in remission from her cancer.

2.2. Case 2

The second case is a 70-year-old nulliparous female who was a living kidney transplant donor to her brother. A CT renal angiogram performed, for donor assessment, revealed an incidental finding of prominently enlarged retroperitoneal lymph nodes, without other significant lesions. A positron emission tomography (PET)-CT performed 1 year later revealed several hypermetabolic retroperitoneal nodes up to the

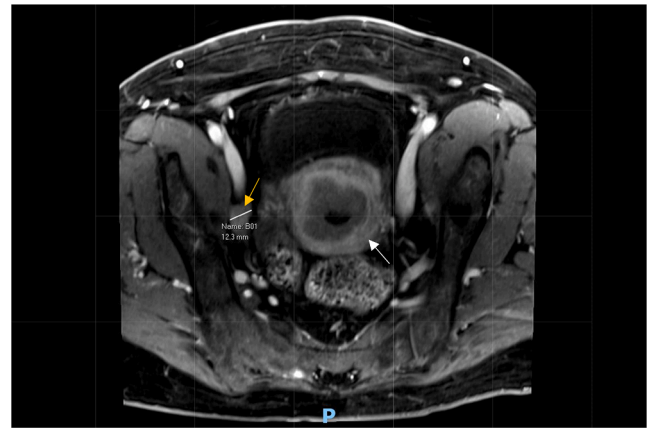


Fig. 2. MRI pelvis scan showing enhancing endometrial mass involving outer half of myometrium (white arrow), with pelvic nodule (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

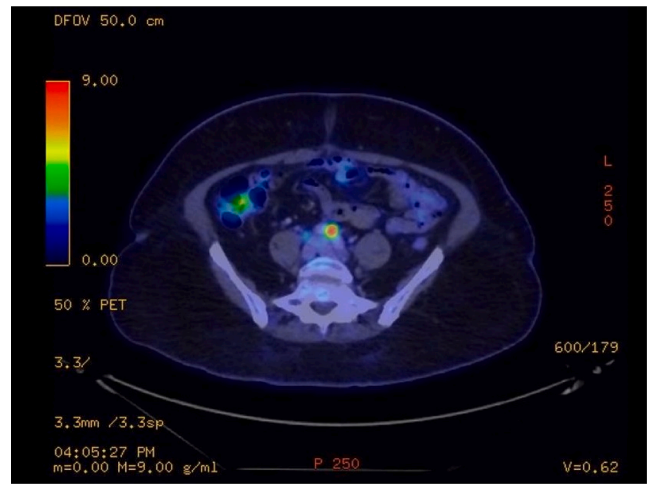


Fig. 3. PET-CT scan showing hypermetabolic retroperitoneal lymph nodes, suspicious for nodal disease.

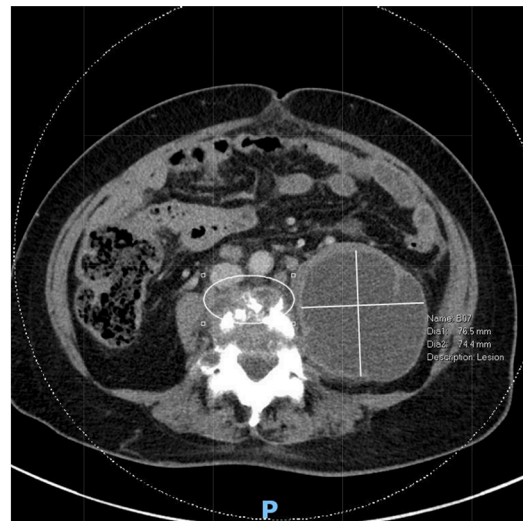
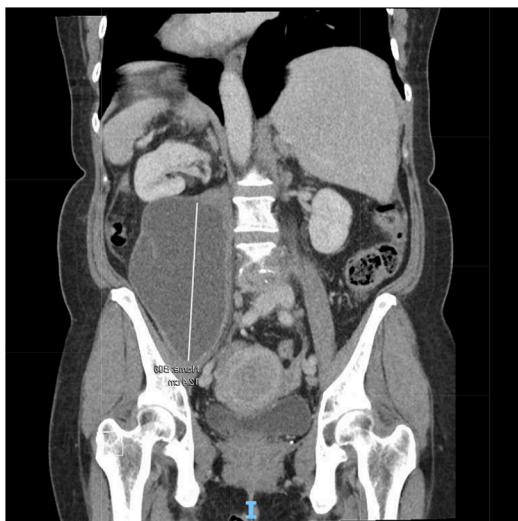


Fig. 1. CT TAP coronal and transverse scans showing left psoas abscess with adjacent L3-4 spondylodiscitis (white oval), with heterogenous lesion seen in the endometrial cavity.

level of the renal hila and bilateral common iliac nodes, which were suspicious for nodal disease (Fig. 3). Moreover, an intensely hypermetabolic lesion centred in the endometrium was suspicious for a neoplastic process. In her clinical follow-up visits, this patient had no complaints of post-menopausal bleeding, per-vaginal discharge or constitutional symptoms. Her latest Pap smear at this point was negative.

Subsequent endometrial sampling showed FIGO grade 1 endometrioid carcinoma. This patient eventually underwent TAHBSO, with systematic bilateral PLND and PALND. Intraoperatively, a uterus of 6 weeks' size was found, with enlarged *para*-aortic lymph nodes which were dissected up to the level of the renal vein. Bilateral ovaries, fallopian tubes, cervix, bladder, omentum and liver were grossly normal. No enlarged pelvic lymph nodes were seen.

Post-operative histology confirmed FIGO grade 1 endometrioid adenocarcinoma of the uterus, with no myometrial invasion seen (pT1a). Bilateral pelvic lymph nodes were negative for metastases. The *para*-aortic lymph nodes showed evidence of granulomatous lymphadenitis with necrosis and were negative for metastases. TB polymerase chain reaction (PCR) analysis of the affected lymph nodes were negative. However, this laboratory test has not been validated for formalin-fixed specimens and correlation with other clinical or radiological findings was necessary. Given the histological results, a referral was made to the Infectious Diseases team for TB, who was keen to start anti-tuberculosis treatment, but the patient refused. Currently, the patient remains in remission from her cancer. In subsequent clinic follow-ups, the patient had no constitutional symptoms and surveillance CT scans showed no recurrence of lymphadenopathy or tumours.

2.3. Case 3

The third case is a 63-year-old para 1 female. This patient had a known history of rheumatoid arthritis, on oral prednisolone 5 mg as required. She was referred from the Rheumatology department for post-menopausal bleeding. Endometrial sampling performed showed a FIGO grade II endometrial cancer. Concurrently, a small bowel gastrointestinal stromal tumour (GIST) was diagnosed.

A CT chest and abdomen showed right upper lobe subpleural nodule with ground glass changes and apical scarring. An MRI pelvis showed a thickened and irregular endometrium at the uterine fundus likely representing the site of primary malignancy, possibly > 50% myometrial invasion (Fig. 4), with left external iliac adenopathy and right external iliac and right obturator lymphadenopathy. There was also avascular necrosis of both femoral heads.

This patient underwent TAHBSO with bilateral PLND, PALND and bowel resection. Post-operative histology showed mixed high-grade



Fig. 4. MRI pelvis sagittal scan showing irregularly thickened endometrium at uterine fundus (white arrow), likely primary site of malignancy.

serous (90%) and endometrioid (10%) carcinoma of the endometrium. Final histology of the GIST tumour showed a 4 cm tumour, low grade with low risk of progressive disease and with clear resection margins. Lymph nodes obtained from the right obturator and common iliac lymph nodes showed granulomatous inflammation with necrosis. Acid fast stain and TB PCR for these lymph nodes were negative for TB. In view of the overall clinical picture with granulomatous lymph node changes, apical scarring with an indeterminate nodule and positive Tuberculin Skin Test, a presumptive diagnosis of APTB was made by the Infectious Diseases physician. The patient was treated empirically with isoniazid, pyrazinamide, ethambutol and levofloxacin. A multidisciplinary tumour board meeting concluded that the patient had stage 2 (cervical involvement), grade 3 (serous) endometrial cancer. This patient completed chemotherapy (paclitaxel and carboplatin), small-field radiotherapy and brachytherapy. Currently, the patient is in remission and subsequent surveillance CT scans showed no recurrence of cancer or lymphadenopathy.

3. Discussion

APTB most commonly presents with abdominal pain (95%), weight loss (88%), fever (84.6%), abdominal mass (46.1%), and other symptoms including, but not limited to, constipation, vomiting/nausea, abdominal pain, with possible signs of ascites and peritonitis (Hossain et al., 2012). These presenting clinical features may mimic advanced gynaecological cancers, notably of ovarian origin, making diagnosis of either condition difficult. To date, many authors have reported cases of ovarian cancer with co-existent tuberculosis, describing similar diagnostic and therapeutic conundrums (Sharma et al., 2010; Koc et al., 2006; Gupta et al., 2016). However, to the best of our knowledge, there have only been two case reports documenting coexistent endometrial cancer with APTB (Saygili et al., 2002; Castelo-Branco et al., 1995).

The FIGO classification stages endometrial cancer based on surgical-pathological findings. For patients diagnosed with endometrial cancer, a TAHBSO, PLND and/or PALND or omentectomy is performed depending on histological results. However, there has been a lack of consensus on the utility of systematic lymph node dissection in patients with endometrial cancer. Although retrospective data suggests that systematic lymphadenectomy improves survival compared to limited lymphadenectomy or no sampling, the results of two randomized controlled trials did not show any benefit in terms of disease-free and overall survival (Franchi et al., 2020). Furthermore, surgical lymphadenectomy is a specialized technique that is costly and time-consuming, which also increases the risk of immediate and delayed surgical complications (Kitajima et al., 2011). This has led to alternative methods of ascertaining nodal status such as non-invasive imaging scans and sentinel lymph node biopsy (Franchi et al., 2020). Regardless, accurate staging of endometrial cancer is important for proper diagnosis, treatment and prognostication. As demonstrated by the above cases, PLND/PALND is paramount to avoid inaccurate staging of endometrial cancer.

To circumvent the surgical morbidity and debatable survival benefit of PLND/PALND, some have considered the use of PET-CT scanning as an alternative staging technique in the context of endometrial cancer (Franchi et al., 2020; Suga et al., 2011; Crivellaro et al., 2013). The high positive predictive value (91.7%) of the scan may be beneficial to surgeons when selecting appropriate patients for lymphadenectomy (Crivellaro et al., 2013). However, there is a risk of over-staging as imaging modalities cannot accurately confirm the aetiology of enlarged lymph nodes. In the example of Case 2, the patient's PET-CT scan was reviewed by various medical professionals including radiologists, renal transplant, urology and gynaecology specialists. The consensus was that the PET-CT showed retroperitoneal lymph nodes metastases from an endometrial cancer primary, as endometrial fluorodeoxyglucose (FDG) uptake was similar to the retroperitoneal lymph nodes. Moreover, common sites for metastatic endometrial cancer are the retroperitoneal lymph nodes below the level of the renal vein. Regardless of the initial impression,

comprehensive surgical staging was performed. In contrast to the radiological consensus, lymph node histology showed no nodal metastases, which translated to a Stage 1 endometrioid adenocarcinoma. Without surgical staging, presumptively treating the cancer as Stage 3C2 would have resulted in avoidable treatment-related complications, including chemotherapy which may further cause immunosuppression, which may severely impact the morbidity or mortality of tuberculosis patients. While these instances are rare, they warrant attention as the medical consequences on these patients can be quite significant.

Case 3 further emphasises the importance of accurate staging of endometrial cancer. The MRI pelvis reported > 50% myometrial invasion, which correlates with a six- to sevenfold higher prevalence of pelvic and *para*-aortic lymph node metastasis, and advanced surgical staging. In such cases, it is recommended to perform more aggressive surgical staging (Larson et al., 1996). The aetiology of lymphadenopathy for Case 3 was tuberculous rather than malignant in origin, confirmed on histological analysis of lymph node dissection. Therefore, localised vaginal vault radiotherapy was commenced. Conversely, if only radiological staging was used, clinicians may be misled to diagnose a Stage 3C2 endometrial cancer, requiring radiotherapy to the pelvic and *para*-aortic regions. The additional side effects from more aggressive radiotherapy may potentially lead to worse patient outcomes.

The utility of PET scans to replace surgical staging has also been extrapolated to cervical cancer and some cases of unexpected diagnosis of endometrial cancer following hysterectomy for benign conditions. In patients with PET evidence of pelvic lymphadenopathy, they would be automatically upstaged to 3C2 although the aetiology of the lymphadenopathy is unconfirmed. These patients may therefore require extended field of radiotherapy and may be deemed unsuitable for further surgical therapy. Lymph node histology could be obtained through interventional radiology-guided biopsy, but may be limited by challenging access, especially for retroperitoneal lymph nodes. An alternative option is lymph node dissection, although treatment may be delayed, requiring technical expertise, with increased surgical morbidity.

Case 1 illustrates an additional learning point regarding the presence of peritoneal disease in endometrial cancer. In general, a pre-existing gynaecological cancer with peritoneal lesions may suggest carcinomatous peritonei, or more specifically stage 4 disease in the context of endometrial carcinoma. The appropriate management of the above would be either (1) debulking surgery, which would pose significant surgical morbidity for the patient, or (2) palliative TAHBSO, which may involve significantly less surgical dissection but is associated with less surgical morbidity. In Case 1, however, intraoperative frozen section analysis revealed the presence of miliary TB rather than metastatic spread. The operating surgical team was thus well-informed to proceed with complete surgical staging, which confirmed a stage 3C1 endometrial carcinoma. The patient was subsequently treated appropriately with chemotherapy followed by pelvic radiotherapy to improve survival benefit. This case emphasizes the advantage of access to intraoperative frozen section analysis in guiding the surgical team regarding the extent of surgery during the surgery itself.

Additional precautions during surgery have been recommended for patients with pulmonary TB to prevent transmission to healthcare workers. However, patients with APTB can be considered non-infectious when they meet the following 3 criteria: (1) 3 consecutive negative AFB sputum smears collected in 8- to 24-hour intervals (one should be an early morning specimen); (2) compliant with an adequate treatment regimen for two weeks or longer; and (3) clinical improvement of symptoms (Jensen et al., 2005). Knowledge of this aids in the scheduling of surgery for these patients and avoids unnecessary postponement of surgical procedures which may lead to progression of disease.

4. Conclusion

In summary, co-existent APTB with endometrial carcinoma is a rare

entity, though its possibility should be strongly considered in TB-endemic regions and in the context of endometrial malignancy with abdominopelvic lymphadenopathy. A missed diagnosis of co-existent APTB may result in vastly different post-surgical therapeutic regimens, leading to poor quality of life for patients. In a similar vein, understaging of endometrial carcinoma for patients with known APTB, in the form of inadequate PLND, may lead to inadequate management of the carcinoma. Given the lack of discriminatory pre-operative diagnostic techniques to distinguish APTB from endometrial carcinoma, we would strongly recommend comprehensive surgical staging with intraoperative frozen section analysis, to ensure accurate cancer staging and thorough treatment of TB. Although this may confer additional surgical morbidity to the patient, the greater consequences of over-staging, misdiagnosis and mismanagement must be considered. Moving forward, there is scope for further research to better distinguish between APTB and metastatic gynaecological cancer, and further elucidate the immunosuppressive relationship between TB and endometrial carcinoma.

Ethics approval and consent to participate

Not applicable

Consent for publication

A written informed consent for publication was obtained from all participants

Availability of data and materials

Not applicable.

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Authors' Contributions

Performed data acquisition and writing of report: Muhammad Ashraf Yusoff, Goh Wei An, Tan Mei Xin Eunice.

Made contributions to conception of the study, editing and review of the report: Ravichandran Nadarajah.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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