Case Report

SAGE Open Medical Case Reports

The haunting diagnosis of malignancy in women with treatable reproductive system tuberculosis

SAGE Open Medical Case Reports
Volume 11: 1–4

DOI: 10.1177/2050313X231184958
journals.sagepub.com/home/sco
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Abstract

This study reports a case of female genital tuberculosis in a 46-year-old woman who presented to emergency department with abdominal pain and progressive abdominal distension. The patient was initially thought to have ovarian cancer based on clinical diagnosis and elevated cancer antigen-125 (CA-125) levels. Intra-operatively, no obvious ovarian tumor was encountered instead; disseminated creamy white patches on the uterus and left adnexa were seen. About 4500-mL straw-colored ascitic fluid and disseminated creamy white patches were also found on the bowels and omentum giving an impression of carcinomatosis. However, histopathology of the fallopian tube and ovary confirmed the diagnosis of female genital tuberculosis as the underlying cause. Female genital tuberculosis often mimics tumors in its clinical appearance and symptoms, leading to misdiagnosis and unnecessary treatment. The key to diagnosing female genital tuberculosis is being suspicious as it is challenging to diagnose through laboratory tests or radiology. The mainstay of treatment for female genital tuberculosis is a combination of four antituberculosis drugs. Consideration of female genital tuberculosis as a differential diagnosis in women presenting with symptoms mimicking reproductive tumors is highly recommended as highlighted in this case report.

Keywords

Female genital tuberculosis, diagnostic challenge, ovary, fallopian tube, malignancy

Date received: 10 March 2023; accepted: 12 June 2023

Introduction

Tuberculosis (TB) is an infectious disease that most often affects the lungs and is caused by a type of bacteria (*Mycobacterium* sp.). TB is the most notorious mimic of tumors, or diagnostic chameleons in low-resource settings are TB.[1] Female genital tuberculosis (FG-TB) is a non-neoplastic disease that often resembles tumors affecting the female genital system in terms of their clinical appearance and symptoms.[2] The misdiagnosis FG-TB predisposes the patient to unnecessary surgery and medical treatment. Furthermore, there is an increase in economic burden and psychological stress to TB patients wrongly diagnosed as cancer patients. This necessitates the importance of excluding TB in all patients who presents with condition that mimics TB.

TB remains to be a major global health concern particularly in regions with high incidence of HIV/AIDS. It is the second to COVID-19 as the leading infectious cause of death worldwide. About a quarter of the global population is estimated to have been infected with TB bacteria. About 5%–10% of people infected with TB will eventually get symptoms and develop TB disease. Diagnosis of extrapulmonary TB can be challenging. Unfortunately, there is no peculiar clinical, laboratory, or radiological distinctive characteristics that are sufficient to ascertain the diagnosis of extrapulmonary TB. Thus, advanced gynecological

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malignancies and peritoneal carcinomatosis can easily be mistaken for TB involvement of the gastrointestinal or genital urinary tracts.[3] Clinically, FG-TB presents with vague symptoms of abdominal pain, dyspareunia, abnormal genital tract bleeding, offensive vaginal discharge, menstrual irregularity, menorrhagia, and dysmenorrhea.[4] In some patients, FG-TB can be asymptomatic, while in others it may present with anorexia, episodes of diarrhea and vomiting, weight loss, night sweats, or intermittent fever. Similarly, pelvic pain, infertility, fever, unusual uterine hemorrhage, ascites, and pelvic mass have been reported in patients with FG-TB.[3–6] A tumor marker for ovarian cancer (cancer antigen-125 [CA-125]) may also rise in TB patients, although a pelvic mass with ascites, elevated CA-125 levels, and peritoneal seeding strongly suggest pelvic cancers.

FG-TB may represent up to 20% of extra-pulmonary TB and remains to be a major health problem in most developing countries including Tanzania. However, because of wide spectrum of clinical presentations including asymptomatic, varying imaging and laparoscopic outcomes; as well as contradicting serological and bacteriological test results, the true incidence may be underreported.[3] Thus, it is critically important to have a high level of suspicion with thorough inquiry and investigation. Unfortunately, currently, there is no single 100% accurate diagnostic method for FG-TB. However, different approaches such as the use of endo-ovarian tissue biopsy and pelvic aspirated fluid by conventional and molecular methods have shown some convincing evidence.[7] Thus, scrupulous TB studies are essential for the definitive diagnosis especially in patients with a positive chest X-ray for healed or active pulmonary TB, history of TB contact, an elevated erythrocyte sedimentation rate (ESR), and positive tuberculin skin test. Herein, we report the case of a 46-year-old female patient with a FG-TB and a brief review of the literature.

Case report

A 46-year-old female patient with a P2L2 medical history visited our emergency department due to gradual onset of abdominal pain, which was progressively worsening with time. It was more on the right lower quadrant. Movement and touch exacerbated the pain, while rest provided relief. In addition, the patient had experienced symmetrical abdominal distension for over a month, which was accompanied by early feelings of fullness, nausea, diarrhea, and alternating constipation. No incidents of vomiting, heartburn, yellow discoloration, or swelling in the lower limbs were reported. The patient also reported no respiratory symptoms, such as difficulty breathing or coughing. She denied history of contact TB. Vital signs were measured as follows: temperature of 36.7°C, blood pressure of 116/76 mmHg, pulse rate of 90 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 99% on room air.

On physical examination, the abdomen was distended with normal contour and a small scar in the lower quadrant; normal bowel sounds were heard upon auscultation. Tenderness was noted in the right iliac fossa region, but there were no palpable masses. Both external and internal genitalia were normal upon examination, with a healthy cervix observed. Other systems were unremarkable. The laboratory results showed leukocytosis with a count of 14.5 (4–11) and a predominant 76% of neutrophils, as well as a low hemoglobin level of 10.6 (11.5–16.5). The CA-125 level was elevated to 52.5 (normal range: 0–35 units per mL). The renal and liver function tests, including urea and creatinine levels, were normal. Inflammatory marker C-reactive protein test was high 800 (0.8–3 mg/L). A chest X-ray showed normal results, while the abdominal ultrasound revealed the presence of massive ascites, a suspicious heterogeneous mass in the posterior aspect of the uterus, and mesenteric lymphadenopathies. The findings led to the impression of an ovarian mass and a clinical diagnosis of ovarian cancer. However, due to financial constraints, a computed tomography (CT) scan was not conducted, and no biopsy was performed prior to surgery.

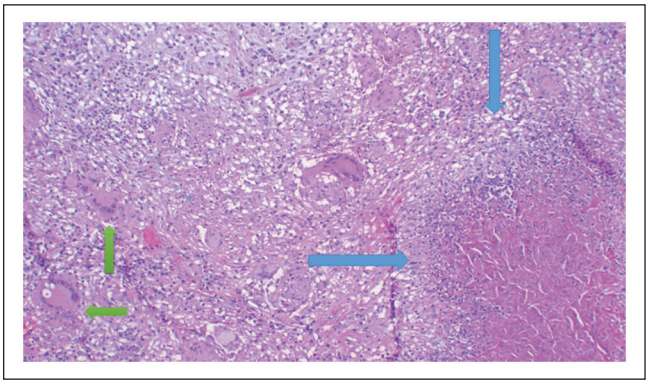

Figure 1. Hematoxylin and eosin-stained photomicrograph showing epithelioid cell granulomas with central caseation (blue arrows) and Langhans type of multinucleated giant cells (green arrows) 100× original magnification.

Intra-operatively, no obvious ovarian tumor was encountered instead; disseminated creamy white patches on the uterus and left adnexa were seen. About 4500-mL straw-colored ascitic fluid and disseminated creamy white patches on the bowels and omentum were evident giving an impression of carcinomatosis. Therefore, diagnosis of ovarian cancer was entertained. The liver and right ovary were essentially unremarkable. Total hysterectomy and partial omentectomy were done, and the specimens were submitted for histopathology analysis. Peritoneal fluid was submitted for cytological analysis and for GeneXpert for the TB. While the GeneXpert results were negative, the histopathological studies of the ovary, endometrium, and fallopian tube revealed numerous caseating granulomatous inflammation with Langhans-type multinucleated giant cells (Figure 1). Similar findings were observed on the omental tissue. Ziehl–Neelsen staining confirmed the presence of acid-fast bacilli (AFB) (Figure 2). Therefore, the final diagnosis of FG-TB was established. The patient was kept on anti-TB rifampicin/isoniazid/pyrizinaamide/efavirenz as well as ceftriaxone and

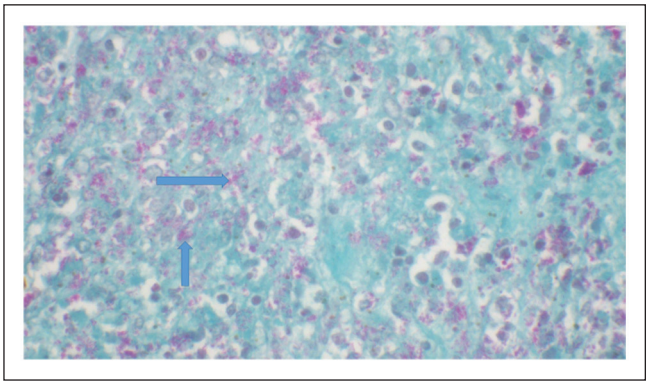

Figure 2. Ziehl–Neelsen histochemical staining photomicrograph of fallopian tube demonstrating foamy macrophages packed with AFB bacteria organisms (blue arrows); 200× original magnification.

antipain medications. She did well immediately after surgery and was discharged on day 5. The patient completely recovered during the 6 months of close follow-up visits and had resumed her daily activities.

Discussion

Diagnosing FG-TB poses significant challenges in terms of costs and time to patients particularly in resource-constraint settings and to health care professionals.[6] Symptoms such as pelvic inflammatory disease, infertility, and gastrointestinal issues like nausea, vomiting, and early satiety raise alarm bells to the clinicians. In addition to menstrual symptoms, patients may also experience typical TB symptoms such as weight loss, night sweats, and fever. An ultrasound can uncover fluid build-up or abnormal results in the female genital tract, with the fallopian tube being the most susceptible to TB. As it was the case in our patient, patients with ovarian TB may present with elevated levels of CA-125, a marker for ovarian cancer.[3]

When patients delay in seeking health care and thus present as an acute abdomen emergency condition, the situation may further pose a significant challenge in diagnosing FG-TB, as evidenced by our case which was initially thought to have ovarian cancer clinically. This scenario is not uncommon, as numerous studies have reported similar phenomenon.[7,8] Our patient experienced an increasing abdominal distention and pain which are common early presentation of FG-TB. In addition, the patient also presented with typical gastrointestinal symptoms such as early satiety, nausea, and vomiting, similar to what has been reported in other cases.[4,6] Our case mirrored others in presenting with ascites on ultrasound, as well as nonspecific abdominal distension, which is frequently seen in FG-TB cases.[9] The elevated levels of CA-125, a marker commonly associated with ovarian cancer, further complicated the diagnosis and initially led to a clinical diagnosis of ovarian cancer. However, there are cases where raised CA-125 levels did not necessarily indicate ovarian cancer.[3] Unlike many other FG-TB cases, our patient did not exhibit menstrual symptoms, despite having endometrial TB. This deviation from the typical presentation seen in other studies highlights the variability and challenges in diagnosing FG-TB.[6,10]

GeneXpert Mycobacterium tuberculosis and resistance to rifampicin (MTB/RIF) system is a cartridge-based nucleic acid amplification test (NAAT) for simultaneous rapid TB diagnosis and rapid antibiotic sensitivity test. World Health Organization (WHO) approved GeneXpert MTB/RIF in 2011 and recommended it for prompt implementation. It is an automated diagnostic test that can identify *Mycobacterium tuberculosis* (MTB) DNA and resistance to rifampicin (RIF) using polymerase chain reaction (PCR). The Xpert MTB/RIF extracts genomic material from the collected bacteria by sonication and subsequently amplifies the genomic DNA by PCR. It purifies and concentrates MTB bacilli from sputum samples. GeneXpert MTB/RIF system has been suggested as a rapid and efficient technique that can detect MTB within short time.[11] The system is easy to use, carries the minimum risk of cross-contamination, and is biosafe with a pooled sensitivity of 88%, 95% confidence interval (CI)=(84%–92%), and a pooled specificity of 99%, 95% CI=(98%–99%), in diagnosis of pulmonary TB. GeneXpert has been used also to evaluate the detection of abdominal TB from ascitic fluid samples and has shown some promising sensitivity.[11] However, some contradictory results are not uncommon. For instance, Pandey et al.[12] reported relatively poor performance of GeneXpert for the detection of TB from extrapulmonary samples. The low test performance observed in these studies could be explained by the fact that extrapulmonary samples are typically paucibacillary, and thus, it is possible that the GeneXpert negative result was caused by lower than the assay's limit of detection for MTB/RIF concentration of MTB in the GeneXpert.

Several reports have shown complications in the diagnosis of FG-TB. For example, people with FG-TB have been managed as lung cancer patients, and ovarian TB has been treated as ovarian cancer.[1] The key to the diagnosis of FG-TB is clinical, radiological, and pathological correlation. For example, a study looking at endometrial TB found inferiority in histopathological diagnosis compared with PCR, where paucity in diagnosing TB is high with use of Ziehl–Neelsen stain and even culture was reported to be challenging in diagnosing FG-TB.[6–9] The mainstay for treatment of FG-TB is daily use of rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol for 2 months, followed by daily therapy with two out of the four drugs: rifampicin (R) and isoniazid (H).[1,7] Our patient had neither personal nor family history of TB, and she had no any conventional TB-related symptoms such as weight loss, night sweats, or fever. This lack of recognizable symptoms adds to the difficulty in diagnosing FG-TB accurately.[13] Currently, there are no 100% accurate diagnostic methods for detecting FG-TB. Therefore, to improve the accuracy of FG-TB diagnosis, high suspicion index is recommended especially in TB-endemic areas. Although GeneXpert techniques have shown some promises, histopathological testing

is essential for the definitive diagnosis, ruling out potential differential diagnoses and, thus, ensuring prompt and proper treatment.[14,15]

Potential caveat for our case study is the lack of essential information such as preoperative investigations such as CT scan, intra-operative images of surgical field, and photographs of the specimens that were submitted for histopathology. This is partly because the patient presented with an emergency situation (acute abdomen) and diagnosis of FG-TB was not considered both prior to surgery and also intra-operatively. The decision that prompted us to undertake hysterectomy surgery was because of intra-operative findings. Obviously, there was no ovarian mass; however, the presence of disseminated white patches (creamy appearance) around the bowels and omentum, as well as frozen left ovary and fallopian tube, and intra-abdominal lymphadenopathy painted a false picture of left ovary cancer (carcinomatosis); considering the patient had elevated CA-125. The discrepancy between the preoperative and postoperative diagnosis observed in the index case implies that preoperative screening and the diagnosis were inadequate thus led to the patient's suboptimal treatment.

Conclusion

In conclusion, FG-TB is a disease that may easily be misdiagnosed as a tumor due to its similar clinical appearance and symptoms. This misdiagnosis can lead to unnecessary treatments, costs, and added stress to patients as it was the case in our patient. Therefore, it is very important for health care providers to consider FG-TB as a differential diagnosis in women presenting with symptoms that mimic gynecological tumors. The definitive diagnosing this challenging entity is combination of laboratory tests, radiology, and histopathology.

Acknowledgements

We would like to thank the patient for allowing us to use her medical information for academic purpose in this publication and surgeons who did the operations.

Author contributions

A.M. contributed to conception and writing original draft; J.J.P. contributed to review and data presentation; P.A. and E.R.S. contributed to editing and improving clarity; A.A.A. contributed to case acquisition and review; G.N. contributed to case acquisition and review and editing; U.J. contributed to data presentation; A.P. contributed to conception and writing original draft.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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