



Case Report

Female genital tuberculosis presented with primary infertility and persistent CA-125 elevation: A case report

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ABSTRACT

Introduction: and importance: Tuberculosis is one of the leading causes of mortality in many developing countries. Female genital tuberculosis, a relatively uncommon form of tuberculosis, is critically challenging to diagnose due to its insidious and non-typical presentations.

Case presentation: Herein, we present with an asymptomatic infertile woman with persistently high CA-125 passed undiagnosed until laparoscopy unveiled the diagnosis of TB.

Clinical discussion: In this study, we highlight the diagnostic complexities in female genital tuberculosis and demonstrate the value of the CA-125 increase in prompting the suspicion of tuberculosis in the appropriate clinical context.

Conclusion: Given the considerably large number of individuals with tuberculosis in China, we strongly recommend routine tuberculosis screening in women seeking infertility care in China.

1. Introduction

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis*. It represents a significant public health burden secondary to high prevalence in developing countries and enormous health care utilization and spending. Globally, it was ranked as top 13 causes of mortality, accounting for 1.5 million deaths in 2020 [1]. TB predominantly infects the lungs, but it also occurs in extrapulmonary sites via the hematogenous or lymphatic route.

Female genital TB (FGTB) is a relatively rare form of TB, consisting of 9% of all extrapulmonary TB [2]. FGTB has a detrimental impact on female fertility by distorting tubal structure and mobility, damaging the endometrial lining and resulting in intrauterine adhesions, and depleting ovarian reserve via chronic inflammation. Besides compromising fertility, TB during pregnancy is associated with severe adverse maternal outcomes, with a 2.8-fold increased maternal morbidity risk in comparison with those healthy pregnant women [3]. Similarly, the neonatal complications delivered by women with TB are deleterious,

too; their odds of delivering babies of lower birth weight are nearly doubled, and the odds of experiencing perinatal death are about 4 times greater compared with TB-free pregnant women [3]. To prevent these maternal and fetal outcomes attributed to TB, early diagnosis is the key.

Herein, we report an asymptomatic infertile woman with continued elevated CA-125 going through extensive workups to screen malignancy but turned out to be diagnosed as FGTB. We demonstrate that persistent raised CA-125 can be misleading and often result in misdiagnosing TB patients as malignancy. We highlight that continued CA-125 increase may indicate the presence of TB, especially when typical clinical manifestations and suggestive TB imaging findings are lacking.

2. Case report

A 35-year-old nulligravida Chinese woman presented to our gynecology outpatient clinic with a 9 years history of primary infertility. Her menstrual cycle had been regular without dysmenorrhea and disturbance in the bowel and bladder. Five years ago, the

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hysterosalpingography she took revealed her left fallopian tube was obstructed while the right was patent, prompting her to undergo fallopian tube recanalization and pelvic adhesiolysis via laparoscopy; no tuberculosis lesions were identified during the surgery. However, the postoperative ovulation induction using clomiphene citrate with timed intercourse for three cycles had failed in achieving pregnancy.

She had no other family, drug or other medical history of note except an enduring increase in CA-125 level. At the annual physical examination that she took one year before admission, her CA-125 was accidentally found to exceed the upper limit of 35 U/mL. Since then, the serum CA-125 had fluctuated between 70.0 U/mL and 138.6 U/mL; at the same time, her CA-199 had elevated to 47.39 U/mL (normal range 0–37). To exclude malignancy, a gastrointestinal endoscope and pelvic CT scans were performed, both of which were negative in results. Given her history of infertility and a persistently high level of tumor biomarkers, the patient was admitted to the gynecology department of our hospital.

On admission, the patient complained of no discomfort. She denied chronic cough, weight loss, and night sweat. She had not traveled abroad and was unaware of any contact or exposure to TB. On physical examination, her BMI was 20.96 kg/m². The lungs sounded clear on auscultation, and the abdominal and perineum examinations produced normal findings. On vaginal examination, the appearance of the cervix and vagina were all normal without discharge; the uterus was anteverted and in normal size with full mobility, and there was no tenderness or mass in the uterus and adnexa. Her physical examinations on other systems were unremarkable.

Her laboratory investigation was notable for an increased CA-125 at 46.46 U/ml (normal range 0–35U/mL). Other laboratory tumor markers results including alpha-fetoprotein (AFP) and human epididymis protein 4 (HE4) were negative. Her albumin was in the normal range and the laboratory results of liver and renal functions were inconspicuous. The pelvic ultrasound showed a normal uterus at 50 × 45 × 37 mm and a singular intramural fibroid in diameter of 14 × 8 mm; the cervix and ovaries were normal looking, and no fluid was detected in the cul-de-sac. Further imaging included chest radiography, revealing no significant findings. In view of the patient's history of infertility and suspicion of malignancy, she was offered an exploratory laparoscopy combined with a hysteroscopy. The surgery was performed by one of the authors, a senior experienced surgeon who specialized in gynecology.

Prior to the hysteroscopy, we observed the cervix external OS was difficult to be inserted using a 4 mm Hegar dilator; therefore, dilation was completed using 5–7 mm dilators before the hysteroscope could be introduced. Under the hysteroscopic view, the uterine cavity was normal in shape with clear, visible bilateral tubal ostium. No polyps or adhesions were identified. The abnormal finding was that the endometrium was patchy and mottled. Specifically, in the lower, anterior wall of the uterus, the rough, uneven, and reddish color endometrium was observed, while the endometrium in the fundus was thin, smooth, and orangish with small pieces of endometrium-like tissue floating. The floating tissue and the endometrium located at the low, anterior wall of the uterus were biopsied.

Laparoscopically, massive adhesions were seen between bilateral board ligaments, fallopian tubes, and posterior peritoneum. Multiple miliary nodules were observed on the surface of the sacrospinous ligament, rectosigmoid, and cul-de-sac, where a small amount of fluid was identified; the bilateral tubes appeared torturous and rigid. We performed the lysis of adhesions to restore the normal anatomy of the pelvic, and the miliary nodules were excised and biopsied. The histological report revealed chronic granulomatous inflammation with necrosis suggestive of tuberculosis in both the endometrium and fallopian tubes. Postoperative T-SPOT® TB assay (an interferon (IFN)- γ release assay) also reported positive TB findings.

Five days post the surgery, the patient was referred to a local chest hospital where a definitive diagnosis of tuberculosis was established. She has been receiving quadruple anti-TB therapy and planned to return to the infertility center once recovering from TB. The patient considered

the overall diagnosis and treatment were effective; however, she also has had concerns that her chances of getting pregnant will be even lower after she is recovered from the anti-TB therapy. This work has been reported in line with the SCARE 2020 criteria [4].

3. Discussion

Our case emphasizes the diagnostic challenge of FGFB in infertile women with persistent high CA-125 and absence from classic TB presentations. In our patient, she had undergone a gastrointestinal endoscope, pelvic CT scan, and repeated times of tumor biomarkers testing (CA-125, CA-199, and AFP) during a one-year period. It was not until using laparoscopy combined with hysteroscopy—an invasive procedure—did she accidentally receive a correct diagnosis of TB. This difficulty and delay in diagnosis are not only because the pelvic is an atypical location for TB, but because patients often present in the absence of typical TB symptoms such as hot flushes, chronic cough, or weight loss. As the TB progresses, FGFB often has overlapping presentations with ovarian cancers such as weight loss, abdominal pain, and ascites. There have been multiple case reports of FGFB patients misdiagnosed with ovarian carcinoma [5]. Despite pelvic CT scans being sometimes useful in aiding the diagnosis of FGFB, radiological features can be nonspecific or negative, as is shown in our case. These ambiguous presentations and their ability to masquerade other diseases pose a critical challenge for diagnosis, resulting in unnecessary checkups and possibly invasive treatment such as exploratory laparotomy [6].

Our case also highlights the potential for missed diagnosis because of anchoring bias based on the assumption that CA-125 elevation is solely observed in patients with malignancy. Indeed, CA-125 is a glycoprotein with a high molecular weight that is over-expressed by the majority of carcinoma; it is, therefore, most known as a biomarker for cancers, including ovarian cancer, endometrial, peritoneal, and fallopian tube cancers. Nevertheless, it also increases in other benign diseases such as heart failure [7], adenomyosis [8], p125], and fibroids [9], and other inflammatory diseases, such as pelvic inflammatory disease [10]. The mechanisms underlying the pathophysiological link between increased CA-125 levels and the inflammation may be that the inflammatory cytokines including interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), and lipopolysaccharides can act as stimuli to the CA-125 synthesis, with IL-1 being the most potent stimuli during the inflammatory process [11].

Like our patient, CA-125 rise has also been described in patients with TB by other authors [12,13]. For example, a study by Kim et al. prospectively evaluated the serum level of CA-125 in 100 patients with pulmonary TB, and their results showed that CA-125 was increased in 38% of all pulmonary TB cases and the mean of CA-125 was 38.9 \pm 41.4 U/ml with a normal upper limit of CA-125 at 35 U/ml [14]. As a large, public tertiary hospital, using the electronic health record database, we retrospectively searched women of FGFB admitted to the gynecology ward between January 2016 to December 2021. Our results showed that among 19,135 women undergoing either laparoscopy or hysteroscopy, five women with FGFB were identified, all of which were presented with an increased level of CA-125. Importantly, they were all initially misdiagnosed as malignancy, and the diagnosis of TB was revealed only after the surgery was performed (Table 1). Therefore, despite that CA-125 rise is found in up to 90% of patients with ovarian cancers and a proportion of healthy individuals, our case underlines the importance to consider TB in young female patients when they presented with continued raised CA-125, regardless of the presence of abdominal discomforts and positive radiological imaging findings, as described in our case. This anticipation of TB diagnosis before the surgery allows the clinicians to discuss surgical procedures and postoperative care. Of note, establishing the diagnosis of TB early is especially important for infertile women of advanced age. This is because the regimen for treating TB can be as long as 9 months, thereby delaying the fertility assessment and treatment when the expedited approach is needed for women of advanced age.

Table 1

A summary of female genital tuberculosis admitted to the gynecology department of our hospital.

Patient	Age at admission	Patient complaints	Respiratory symptoms at admission	Presence of fever at admission	X-ray results at admission	Diagnosis before surgery	Surgery type	Pre-operative CA-125 levels (IU/mL)	Albumin levels (g/L)
A	38	Continued lower abdominal pain for two weeks	Absent	Absent	Reported the thickening of the lung markings at the left lower lobe	Ovarian cancer	Laparotomy	591.8	Not available
B	61	Abdominal distension for two weeks	Absent	Absent	Suggests the presence of a small amount of pleural effusion	Ovarian cancer	Laparotomy	454.0	31.5
C	42	Abdominal pain for ten days	Absent	Present	Suggests the presence of a small amount of pleural effusion	Ovarian cancer	Laparotomy	240.0	26.4
D	60	Persistent vaginal bleeding after menopause	Absent	Absent	Suggests the enlarged heart shadow	Endometrial cancer	Hysteroscopy and endometrial biopsy	121.2	42.3
E	33	Abdominal distension for one month	Absent	Absent	Suggests the presence of a small amount of pleural effusion	Ovarian cancer	Laparotomy	433.5	26.9

China is one of the 30 high TB burden countries identified by the World Health Organization, with the incidence varying significantly between regions, ranging from less than 30/100,000 in Shanghai to over 180/100,000 in Xinjiang [15]. Worldwidely, the number of individuals with latent TB infection in China is also the highest, with a staggering 350 million infections that are at risk for active TB disease [16]. Yet, TB testing is neither routinely performed in infertility centers in China, nor does there exist domestic guideline concerning TB screening for this population. A Chinese study by Zhang et al. reported two women with TB successfully conceived via in vitro fertilization (IVF); however, both of their babies died 56 days after the birth due to respiratory disorders with one infant confirmed with the diagnosis of TB. Not surprisingly, TB screenings were not prescribed in both of the mothers before the initiation of IVF [17]. Therefore, considering the potential deleterious maternal and neonatal outcomes of women with TB if passed undiagnosed, the high prevalence of TB in China, and the enormous number of Chinese women receiving infertility care every year, we strongly propose that TB screening should be mandated for all women seeking infertility evaluation and treatment in China. The number needed to treat (NNT) to prevent a missed FG TB among infertile women using the QuantiFERON-TB Gold test was 14, a number that was based on the result of a study conducted at an academic fertility center in the US. In the absence of evidence related to the NNT in the China setting, we speculate that this number is lower for Chinese infertile women, given that China has a far higher TB prevalence rate than the US; however, further studies evaluating the cost-effectiveness of TB screening among Chinese infertile women are needed to confirm our speculation.

In summary, our work adds to the existing evidence that CA-125 should no longer be solely considered as a conventional biomarker only for malignancy or endometriosis. A critical learning point from our study is that the diagnosis of TB should be anticipated when asymptomatic patients present with persistent elevated CA-125, especially in TB prevailing regions.

Institutional review board statement

Not applicable.

Data availability statement

Not applicable.

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Ethical approval

Ethical approval was waived by the ethics committee of The People's Hospital of Guangxi Autonomous Region due to its publication type as a case report.

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Author contribution

Conceptualization, Q.F. and L.L.; investigation, X.H. and J.Z.; writing—original draft preparation, J.H. and Q.F.; writing—review and editing, Q.F., J.Z., X.H., J.H. and L.L.; project administration, X.H. and L.L. All authors have read and agreed to the published version of the manuscript.

Trail registry number

1. Name of the registry:

Not applicable.

2. Unique Identifying number or registration ID:

Not applicable.

3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Not applicable.

Guarantor

The Guarantor for this work is Dr Li-ling Liu, who is the correspondent author and can be reached via email by liulilingnn@126.com.

Consent

The patient's written consent to publish this study was obtained.

Declaration of competing interest

No conflict of interest to declare for all authors.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.103683>.

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