

Pregnancy in a patient with endometrial tuberculosis by in vitro fertilization: a case report

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Abstract

Female genital tuberculosis is an important cause of infertility in developing countries where tuberculosis is endemic. However, the true incidence of genital tuberculosis is unknown because symptoms and signs are usually minimal, making its detection difficult. We herein report a case of subfertility due to endometrial tuberculosis. The patient had primary infertility and planned to utilize assisted reproductive technology because of bilateral fallopian tube obstruction. She underwent hysteroscopy and endometrial biopsy. The biopsy revealed epithelioid cells and multinuclear giant cells in the interstitium, and tuberculosis of the endometrium could not be excluded. Chest computed tomography showed secondary pulmonary tuberculosis in the upper left lung. A tuberculin test was positive, and a sputum culture of *Mycobacterium tuberculosis* was negative. The clinical diagnosis was secondary pulmonary tuberculosis. Considering the above findings in combination with the endometrial biopsy results, we concluded that the patient had endometrial tuberculosis. She underwent antituberculosis treatment for 6 months, after which the endometrial tuberculosis resolved and she achieved pregnancy by in vitro fertilization.

Keywords

Infertility, endometrial tuberculosis, antituberculosis treatment, in vitro fertilization, *Mycobacterium tuberculosis*, endometrial biopsy

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Introduction

Tuberculosis continues to be a major worldwide health problem and affects about 10 million people annually. Tuberculosis is one of the top 10 causes of death and the leading cause from a single infectious agent

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(*Mycobacterium tuberculosis*), ranking above HIV/AIDS. About 866,000 new tuberculosis cases and 37,000 tuberculosis deaths occurred in China in 2018.¹ Today, the principal cause of human tuberculosis is *M. tuberculosis*. *Mycobacterium tuberculosis* is a facultative intracellular acid-fast gram-positive pathogenic bacterium capable of producing both progressive disease and an asymptomatic latent infection.²

Apart from the most common and most infectious type of pulmonary tuberculosis, extrapulmonary tuberculosis is being increasingly encountered throughout the world.³ Genital tuberculosis usually occurs secondary to pulmonary tuberculosis, most commonly by the hematogenous route in a manner similar to the spread to other extrapulmonary sites such as the urinary tract, bones, and joints. The fallopian tubes are affected in almost all patients, followed by the endometrium in 50% of patients, ovaries in 20%, cervix in 5%, and vagina and vulva in <1%.⁴ However, a few reports have described the endometrium as the most commonly involved site.⁵ Genital tuberculosis predominantly affects individuals aged <40 years, and the peak incidence occurs from 21 to 30 years of age.⁶ The prevalence of genital tuberculosis varies from 1% to 19% depending on the country. The rate might be even higher among patients with tubal factor infertility (39%–41%).⁷

Infertility is defined as no conception after 1 year of unprotected intercourse.⁸ Infertility is the most common symptom associated with genital tuberculosis.⁹ Genital tuberculosis is typically asymptomatic and is usually diagnosed incidentally during infertility investigations.¹⁰ In many developing countries, genital tuberculosis is responsible for a significant proportion of women presenting with infertility.¹¹ There is a high incidence of endometrial involvement in genital tuberculosis.¹² We herein present a case of endometrial tuberculosis with bilateral fallopian tube

obstruction in a 29-year-old woman. This case illustrates that patients with endometrial tuberculosis require early diagnosis and early treatment of fertility problems.

Case report

Female profile

A 29-year-old woman was referred to our clinic with a 7-year history of primary subfertility. She was intending to undergo assisted conception treatment. Menarche had begun at 15 years of age, and she menstruated for 4 days in a regular 28- to 32-day cycle. Her menstrual flow was unremarkable. She had no hypertension, diabetes, or obesity and had no family members with a similar history. She had no vaginal itching, dysmenorrhea, dyspareunia, or abnormal vaginal discharge. She denied any fever, cough, or chest pain. Her body mass index was 19.28 kg/m². She had a normal pulse rate of 80 beats/minute and blood pressure of 115/76 mmHg. A general physical examination revealed normal findings with no palpable lymph nodes, and a systemic examination showed no abnormalities. A transvaginal study showed a normal vagina and vulva and a normally sized uterus. The results of routine biochemical tests were within the normal range, and the patient's hormonal profile was also normal. However, hysterosalpingography revealed that both fallopian tubes were blocked. To further aid in the investigation and diagnosis, hysteroscopy was performed. An endometrial biopsy was taken and sent for histopathological examination. The biopsy revealed epithelioid cells and multinuclear giant cells in the interstitium, and tuberculosis of the endometrium could not be excluded (Figure 1). The patient was transferred to a local tuberculosis specialty hospital for further diagnosis. Chest computed tomography (CT) showed secondary pulmonary tuberculosis in the upper left

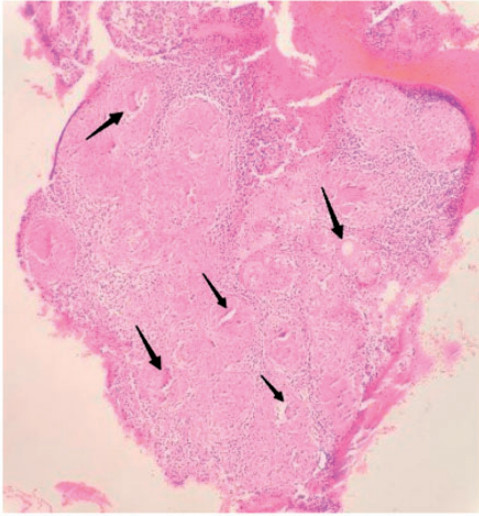


Figure 1. Histologic examination. Epithelioid cells and multinuclear giant cells are seen in the interstitium, and tuberculosis of the endometrium cannot be excluded.

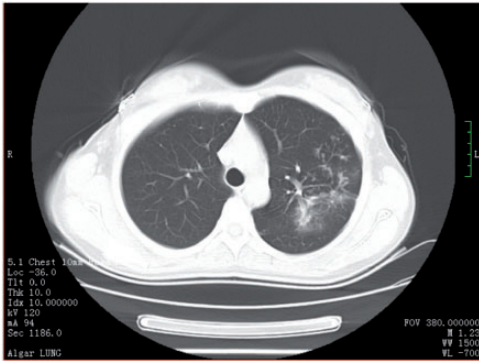


Figure 2. Chest computed tomography. Secondary pulmonary tuberculosis is present in the upper left lung.

lung (Figure 2). A tuberculin test was positive, and a sputum culture of *M. tuberculosis* was negative. The clinical diagnosis was secondary pulmonary tuberculosis. Considering the above findings in combination with the endometrial biopsy results, we concluded that the patient had endometrial tuberculosis.

Male profile

The patient's husband was 30 years old, and his semen analysis was normal. The semen analysis report showed the following findings: days of abstinence, 5; volume, 3.4 mL; liquefaction, normal; color, gray-white; pH, 7.4; sperm concentration, $21.3 \times 10^6/\text{mL}$; and vitality, 53.0%. The morphological analysis report showed the following findings: head defects, 38%; mid-piece defects, 14%; tail defects, 1%; head, mid-piece, and neck defects, 20%; multiple defects, 10%; and percentage of overall defects, 83%.

Treatment

Following the diagnosis of tuberculosis, the patient was referred to a physician for tuberculosis treatment, and plans for assisted reproductive technology were deferred. A 6-month regimen of antitubercular therapy was begun for the patient's endometrial tuberculosis. An initial 2-month intensive phase of four drugs (rifampicin at 600 mg once daily, isoniazid at 300 mg once daily, pyrazinamide at 1500 mg once daily, and ethambutol at 750 mg once daily) was followed by a 4-month course of two drugs (rifampicin at 600 mg once daily and isoniazid at 300 mg once daily). She was compliant on all medications and experienced no adverse effects. Six months later, another endometrial biopsy revealed that the endometrium was in the advanced hyperplasia-early secretory stage (Figure 3). Chest CT showed calcification of the upper left lung (Figure 4). The results indicated that the tuberculosis had been cured.

Ovarian stimulation protocol and fertilization

A long-term plan of assisted reproductive technology was implemented. Pituitary suppression was achieved with subcutaneous administration of a gonadotropin-releasing hormone agonist (0.05 mg of triptorelin;

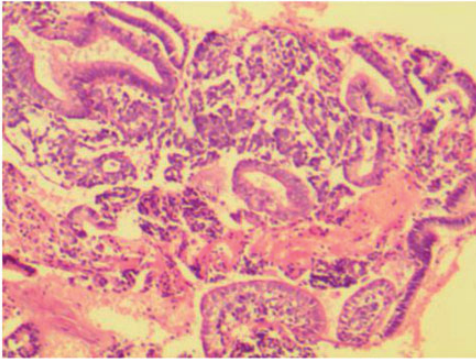


Figure 3. Histologic examination. The endometrium is in the advanced hyperplasia–early secretory stage.

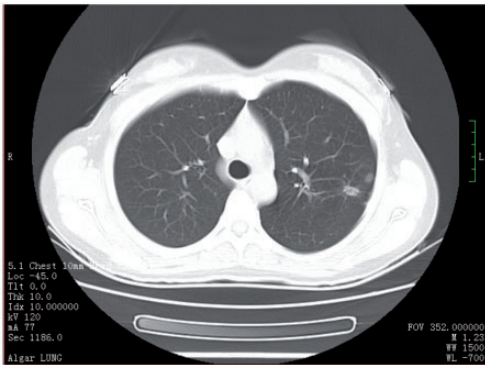


Figure 4. Chest computed tomography. Calcification is present in the upper left lung.

Ferring Pharmaceuticals, Saint-Prex, Switzerland) starting in the midluteal phase. Follicle-stimulating hormone (Gonal-f; EMD Serono, Darmstadt, Germany) was administered for ovarian stimulation starting at 150 IU/day; 5 days later, the dose was adjusted according to the ovarian response. After 9 days of stimulation, the patient received 10,000 IU of human chorionic gonadotropin. At that point, she had six follicles ranging from 14 to 20 mm in diameter, and her estradiol level was 4219 pg/mL. Transvaginal oocyte aspiration was performed 36 hours later, followed by intracytoplasmic sperm injection. At the time of oocyte retrieval, six

oocytes were retrieved, among which four oocytes were normally fertilized and cleaved. On day 3, two embryos were transferred.

Patient follow-up

The patient delivered a normal male infant weighing 3050 g at term.

Discussion

Female genital tuberculosis is a prevalent infectious disease in developing countries where pulmonary tuberculosis is widespread. An estimated 5% to 10% of infertile women worldwide have genital tuberculosis, although this varies from <1% in the United States to nearly 18% in India.¹³ Patients with female genital tuberculosis are usually in the reproductive age group. More than 90% of patients with female genital tuberculosis are <40 years of age, which indicates the hormone-dependent nature of the disease.^{14,15} Consistent with this, our patient was 29 years of age.

Tuberculosis is most commonly localized to the lungs and is caused by the bacterium *M. tuberculosis*. Genital tuberculosis generally occurs secondary to pulmonary tuberculosis (most commonly) or extrapulmonary tuberculosis in sites such as the gastrointestinal tract, kidneys, skeletal system, meninges, or throughout the body (miliary tuberculosis) through hematogenous and lymphatic routes.^{3,16} The endometrium is involved in approximately 50% to 60% of women with genital tuberculosis.⁷ The fallopian tubes are bilaterally involved in up to 80% of cases. Our patient may be a good example. *Mycobacterium tuberculosis* first causes tuberculosis and then spreads through the hematogenous route to the endometrium, resulting in the development of endometrial tuberculosis with involvement of the bilateral fallopian tubes, leading to infertility.

Infertility is the most common presentation of genital tuberculosis because of the

involvement of the fallopian tubes (blocked and damaged tubes), endometrium (nonreception and damaged endometrium with Asherman's syndrome), and ovaries (damage-induced poor ovarian reserve and volume).^{16,17} The diagnosis of female genital tuberculosis is challenging because of the low specificity of clinical symptoms. More than two-thirds of the cases of genital tuberculosis in the literature were diagnosed by histopathological evidence.¹⁸ A positive chest roentgenogram for healed or active pulmonary tuberculosis, a strong contact history, and a positive standard tuberculin test can also aid in the diagnosis.¹⁹ The diagnosis of endometrial tuberculosis remains a difficult task. Any method that is used to diagnose endometrial tuberculosis should be highly sensitive for reliable diagnosis of the disease in its early stage, allowing treatment to improve the prospect of cure before the tubes are damaged beyond recovery.²⁰ In the present study, the patient had been infertile for 7 years. Hysterosalpingography revealed that both fallopian tubes were blocked. A biopsy revealed epithelioid cells and multinuclear giant cells in the interstitium, and tuberculosis of the endometrium could not be excluded. Chest CT showed secondary pulmonary tuberculosis in the upper left lung, and a tuberculin test was positive. Therefore, we were able to definitively diagnose the patient with endometrial tuberculosis.

Treatment of genital tuberculosis does not differ from treatment of pulmonary tuberculosis. Multiple-drug therapy in adequate doses and for a sufficient duration is the mainstay of treatment of tuberculosis, including female genital tuberculosis. Short-course chemotherapy for 6 to 9 months has been found to be effective for medical treatment of female genital tuberculosis.²¹ In our patient, four antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) were given

for 2 months and the first two agents were given for an additional 4 months.²²

Most women with genital tuberculosis present with infertility and have a poor prognosis for fertility in spite of antituberculous therapy. In vitro fertilization (IVF) is a useful treatment that improves the chance of fertility in what was earlier considered a desperate situation. IVF has also provided a ray of hope to desperate infertile women in recent times.²³ Thus, IVF represents the only treatment for tubal and possibly endometrial tubercular infertility. Our patient successfully delivered by IVF. We conclude that IVF is likely to be the most successful treatment for patients with genital tuberculosis, provided that these patients have a normal uterine cavity and functional ovaries.

The purpose of this original case report is to inform all clinicians, particularly those in reproductive medicine, that genital tuberculosis is a diagnosis that requires a high index of suspicion, especially when the patient's history and clinical examination are not suggestive of the disease.²⁴ Early diagnosis and treatment of endometrial tuberculosis is vital to ensure a better prognosis. Treatment is similar to that of pulmonary tuberculosis, although assessing the effectiveness of treatment is difficult because of the lack of clinical and diagnostic criteria for establishment of a cure. Varied evidence exists regarding whether tuberculosis treatment alone will suffice to ensure a return to fertility. IVF with embryo transfer remains the most effective method of treatment associated with infertility.^{25,26} After our patient underwent antituberculosis treatment for 6 months, the endometrial tuberculosis resolved and she achieved pregnancy via assisted conception. IVF and embryo transfer are usually the most suitable options for these patients, as shown in the present case.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics

Written informed consent was obtained from the patient for publication of this case report. The report was approved by the institutional review committee of our hospital.

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