Pregnancy With Atypical Pulmonary Tuberculosis in COVID-19 Outbreak:A Case Report

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Case report

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Abstract

Background

Pregnant women due to reduced resistance, the probability of tuberculosis infection increased, easy to lead to the occurrence of tuberculosis, so pregnancy with tuberculosis is a risk to the health of pregnant women infectious diseases. However, the clinical symptoms of pregnancy with pulmonary tuberculosis are atypical, confused with the physiological reactions of pregnancy, and lack of clinical awareness, especially under the influence of the global COVID-19 epidemic, lung atypical lesions are prone to misdiagnosis or delayed diagnosis.

Case presentation

A 21-year-old woman was infected with *Mycobacterium tuberculosis* during the third trimester of pregnancy. The diagnosis and treatment of the patient were reported.

Conclusion

The interaction between tuberculosis and pregnancy is like a double-edged sword. Raising doctors' awareness on tuberculosis is fundamental, and early diagnosis and standardized treatment are the key to improve the outcome of pregnancy.

Background

Tuberculosis(TB) is one of the most important infectious diseases that endanger all mankind. Nearly one fourth of the world population has TB infection[1]. Statistically, tuberculosis is one of the top three causes of death among women aged 15-45 years[2]. Pregnancy with tuberculosis means that a woman develops tuberculosis during pregnancy or a woman of childbearing age becomes pregnant when tuberculosis is not cured, or is diagnosed with tuberculosis within three months after delivery. It is estimated that more than three million women in the world are infected with tuberculosis and are in the incubation period [3]. About 700,000 women die of tuberculosis each year, and about 26 % of all preventable deaths in pregnancy worldwide are directly attributable to tuberculosis[4]. In China, pregnant patients with tuberculosis account for 2%~7% of the total number of pregnancies[5]. In 2016, Sobhy.S summarized relevant studies on the outcomes of pregnant women with active TB during pregnancy and proposed that active tuberculosis during pregnancy was associated with adverse outcomes in both the mother and the fetus[6]. Under the influence of global COVID-19, pulmonary diseases have attracted more attention. This article reviews the diagnosis and treatment of a case of pregnancy with atypical tuberculosis and the relevant literature to provide reference for the diagnosis of tuberculosis in pregnancy in the future.

Case Presentation

General information and epidemiological history

A 21-year-old woman, weight 55kg, height 160mm, freelance, first pregnancy, at her 28th gestational week. The patient denied having TB, but her husband had the disease and was cured a year ago. The patient had no history of hypertension, diabetes and denied other infectious diseases and chronic diseases. The patient lived in Wuhu for a long time, and denied leaving Wuhu for nearly a month, and denied having contact with COVID-19 patients.

Symptoms and signs on admission

The patient developed cough, sputum and low fever on January 3, 2021. Routine blood examination on January 5 showed that the leukocytes were $7.5 \times 10^9/L$, the percentage of mesenchytes was 85.8%, the percentage of lymphocytes was 9.5%, the neutrophil count was $6.4 \times 10^9/L$, and the lymphocyte count was $0.7 \times 10^9/L$. Abdominal B-mode ultrasonography showed spleen enlargement, no obvious abnormalities in liver, gallbladder, pancreas and kidneys. Cardiac color ultrasonography showed abnormal filling of left ventricle (considered to be caused by tachycardia) and tachycardia (real-time heart rate: 128bpm). The patient was refused a chest imaging examination because of her pregnancy status. The initial diagnosis was "upper respiratory tract infection, bronchitis?".

The patients were given Lianhua Qingwen Granules for detoxification and anti-infection treatment with cefclo for 5 days. Afterwards, the patient had no fever, but the cough did not improve. On January 10, the patient developed dyspnea with progressive aggravation, and was admitted to Yijishan Hospital of Wannan Medical College on January 13. Physical examination on admission: T 36.9°C, P 145 times/min, R 27 times/min, BP 124/97mmHg, SpO₂(73%). Wet rales could be heard in both lungs. Rhythm was uniform, no abnormal heart sounds were heard.

Diagnosis and treatment process

The patient was admitted to the intensive care unit (ICU) unit due to dyspnea and the oxygen of the finger pulse decreased to about 75%. After hospitalization, the patient was given noninvasive ventilator assisted breathing. On January 13th, blood cell analysis showed that leukocyte $8.5 \times 10^9/L$, neutrophil percentage 90.7%, lymphoid cell percentage 7.5%, neutrophil count $7.7 \times 10^9/L$, lymphocyte count $0.6 \times 10^9/L$, hypersensitive C-reactive protein 164.76mg/L, procalcitonin 1.028ng/L. 2019-nCoV nucleic acid test was negative, H1N1 nucleic acid test was negative, HIV antibody test was negative. After considering the adverse effects of radiation and drugs on the fetus, the family members were fully informed of the condition, and the informed consent was signed. Then the chest CT was completed to show the infective lesions of both lungs (Figure 1). The initial diagnosis was "acute respiratory failure, severe pneumonia, 28 weeks of gestation". In view of the fact that the pathogens of pulmonary inflammation are unknown, antiviral (oral oseltamivir 75mg bid), anti-infection (linezolid glucose injection 0.6g q12h, combined with imipenem cilastatin 1g q8h intravenous drip), and maintenance of water and electrolyte balance are given. After two hours of non-invasive ventilator oxygen therapy, the patient's hypoxemia could not be corrected, and the partial oxygen pressure of arterial blood gas was 67.4mmHg. After that, the patient was given invasive ventilator assisted breathing. After the patient's finger oxygen, blood pressure and heart rhythm were stable, bedside fiberoptic bronchoscopy and bronchoalveolar lavage were performed.

During the operation, the right main bronchus and lower lobe bronchus were unobstructed, the mucous membrane was slightly congested, but no obvious sputum was seen; the lumen of the left main bronchus and lower lobe bronchus was unobstructed, the mucosa was slightly congested, transparent exudate could be seen and sucked out under negative pressure. The bronchoalveolar lavage fluid was sent for pathogen examination.

On January 16, the culture results of bacteria and fungi in the lavage fluid were negative. On January 18, sputum smear was positive for acid-fast bacilli, tuberculosis infection T cell test was positive, antigen A hole (119), antigen B hole (92). After 5 days of treatment, the chest tightness of the patient was improved and the vital signs were stable. On January 18, the ventilator was successfully withdrawn and changed to high-flow oxygen inhalation. On January 19th, the patient was transferred to the tuberculosis ward and treated with isoniazid(INH), rifampicin(RFP), ethambutol(ETB) and pyrazinamide(PRZ). The clinical symptoms of the patients were gradually improved, and the fetus developed well and there was no abnormality after monitoring. On January 27th, the re-examination of chest CT, showed that the infectious lesions of both lungs were absorbed than before.(Figure 2). The patient was discharged with medicine on January 29. And on March 10, the culture results of *Mycobacterium tuberculosis* were positive and sensitive to first-line anti-tuberculosis drugs.

Discussion

In China, women of childbearing age receive active attention as a population with a high incidence of tuberculosis. Tuberculosis is also the leading cause of death among women worldwide. According to statistics, more than one million women die every year, among which active tuberculosis is the main cause of maternal mortality[7]. Therefore, it is necessary to raise awareness of the risk of tuberculosis in pregnant women.

The causes of pregnancy with tuberculosis may be the following. Firstly, anti-tuberculosis drugs lead to the decrease of the efficacy of contraceptive. The conventional anti-tuberculosis drug (rifampicin), when used in combination with contraceptive (levonorgestrel), can increase the metabolism of steroid contraceptive and increase the plasma clearance rates of ethinylestradiol and norethisterone[8], resulting in accidental pregnancy during anti-tuberculosis treatment and increasing the incidence of pregnancy with tuberculosis[9]. Secondly, the cellular immune function of the body decreases[2]. The high level of human chorionic gonadotropin in pregnant women can inhibit the immune function of lymphocytes, and the early pregnancy reaction affects the nutritional absorption of pregnant women, resulting in metabolic disorder, and then leads to the decrease of cellular immune function, which is not conducive to the clearance of tuberculosis. Thirdly, the change of endocrine hormone level is affected by the increase of ovarian hormone during pregnancy, which leads to the disorder of autonomic nervous regulation, endocrine and metabolic function, lung hyperemia, upper respiratory tract swelling and so on. And the adrenocortical hormone secretion in pregnant women showed a high level, capillary permeability increased, resulting in easy to be infected by *Mycobacterium tuberculosis* or recurrence of the original tuberculosis focus[10]. Fourthly, in pregnant women, with the increase of circulating blood volume,

microvascular permeability increases gradually, and the upper respiratory tract is congested and swollen, which is very beneficial for tuberculosis bacteria to invade the human body into the blood. Pregnancy causes hypoxia in the lungs caused by the rise of the diaphragm and the decrease of lung dilatation, resulting in lung susceptibility to tuberculosis infection[11]. Fifthly, postpartum tuberculosis infection or recurrence may be caused by rapid changes in hormone levels, changes in cellular immunity, decrease in diaphragm, nutritional consumption and lack of sleep[12].

Tuberculosis is an independent risk factor during pregnancy. Delayed diagnosis remains associated with a substantially elevated risk for poor maternal and fetal outcomes, including a threefold increase in maternal morbidity, ninefold increase in miscarriage, twofold increase in preterm birth and low birthweight, and sixfold increase in perinatal death[6, 13]. Therefore, the key to pregnancy with pulmonary tuberculosis is early diagnosis. However, the diagnosis of tuberculosis during pregnancy is not easy, because the general symptoms after tuberculosis infection are non-specific, mainly manifested as respiratory symptoms and signs: cough, expectoration, hemoptysis, low fever, night sweats, chest pain, shortness of breath and emaciation[7, 14]. It should be mentioned that the symptoms of tuberculosis are easy to be confused with the reaction of early pregnancy. And in the second or third trimester of pregnancy, if patients have cough, chest tightness, chest pain and so on, it is difficult to distinguish them from pregnancy with pneumonia, so it is easy to be delayed by clinicians. The clinical presentation of this patient was similar to the common symptoms of Novel Coronavirus infection (fever, cough, and dyspnea) and was extremely difficult to differentiate from COVID-19 on the basis of clinical presentation alone. Therefore, in order to ensure the health of pregnant women and newborns, it is urgent to make accurate diagnosis as soon as possible for patients with suspected pregnancy with tuberculosis[15]. At present, the diagnosis of tuberculosis is mainly based on the epidemiology, clinical manifestations, imaging, bacterial pathology and immunology. Etiological examination (sputum smear or culture, tuberculosis antigen and antibody detection, etc.), this method is non-invasive and easy to be accepted, and can be used as the first choice during pregnancy, but the sensitivity of acid-fast bacilli staining is low, so more than three sputum examinations are recommended to avoid missed diagnosis. However, the sensitivity and specificity of isolation and culture of tuberculosis bacteria are relatively high, so it is recommended that pregnant women undergo isolation and culture experiment of tuberculosis bacteria, and sputum culture can be used as the gold standard for diagnosis. Blood biochemical and immunological tests (routine blood test, erythrocyte sedimentation rate, cutaneous tuberculin test (TST), tuberculosis T cell dot test (T-SPOT.TB), etc.) , TST have been proved to be safe and effective during pregnancy, and the experimental results are not affected by pregnancy. Chen et al.[16] found that T-SPOT.TB is high sensitivity to the detection of active tuberculosis during pregnancy. It is suggested that interferon gamma release assay (IGRAs) should be used in the clinical practice of screening pregnancy with tuberculosis. IGRAs during pregnancy may be more specific and sensitive than TST, and the experimental results are not significantly related to pregnancy[17], which provides a more accurate method for the diagnosis of pregnancy with tuberculosis. Chest imaging examination (chest X-ray examination, CT examination and magnetic resonance imaging (MRI) examination, etc.), but imaging examinations of pregnant women are rarely performed clinically because of concerns about the effects

of radiation on fetal growth and development. Therefore, imaging examination is only used when pulmonary tuberculosis is highly suspected and requires the informed consent of the patient, in which the diagnostic value of CT is better than that of chest X-ray, while MRI is better for alternative examination in the early stage of pregnancy. The 2004 American College of Obstetricians and Gynecologists (ACOG) guidelines for the diagnosis of pregnancy imaging state that the dose of radiation in diagnostic tests is not sufficient to affect the developing embryo or fetus. If the dose of X-rays during pregnancy is less than 5rad, there is no effect on fetal development. In fact, the exposure dose of diagnostic radioactivity without contrast agent is less than 5rad. The 2016 ACOG guidelines also state that because the amount of radiation used in X-rays, CT scans and nuclear medicine imaging is far lower than the dose that would cause harm to the fetus, there is no need to withhold information from pregnant patients if it is clinically necessary or diagnostic problems can be more easily addressed. The latest guidelines for imaging tests during pregnancy and lactation indicate that imaging tests such as X-rays and CT are safe during pregnancy and lactation, and the radiation dose is far lower than the ionizing radiation dose that can cause damage to the fetus[18]. However, embryos at 8 to 15 weeks of gestation are most sensitive to radiation, and the effect is non-dose-dependent[19]. Therefore, it is necessary to consider the pregnant woman's condition and gestational week comprehensively, and decide whether to carry out radiological examination after weighing the advantages and disadvantages. The laboratory examination of this patient showed that the infection index increased and the lymphocyte count decreased, which was consistent with the changes of SARS-COV-2 infection laboratory examination. The SARS-COV-2 nucleic acid test of pharyngeal swab was performed in this patient, and the results were both negative. Because the nucleic acid test had a certain false negative rate, the serum SARS-COV-2 specific IgM/IgG antibody was detected and the result was negative, so SARS-COV-2 infection was excluded. Although chest CT showed no COVID-19 multiple ground-glass opacity in both lungs, viral pneumonia could not be ruled out. Although the patient had a history of tuberculosis exposure, the diagnostic basis of tuberculosis was insufficient combined with chest CT. So the sputum samples of the patients were taken to detect *Mycobacterium tuberculosis*, the test results was positive, and the results of T-SPOT.TB were positive, which confirmed the infection of tuberculosis.

Pregnancy with pulmonary tuberculosis not only needs early diagnosis, but also needs to grasp the opportunity of treatment. It is generally believed that tuberculosis with standard treatment does not cause adverse effects on the fetus[20]. Delayed diagnosis or non-standard treatment can lead to increased risk of abortion, intrauterine infection, fetal death and intrauterine and neonatal mortality. Jana et al. [20] reported that perinatal mortality increased 5 times in 79 cases of pregnancy with active tuberculosis in India. Figueroa et al.[21] reported that tuberculosis infection during pregnancy increased the morbidity and mortality of newborns, and the later the start of anti-tuberculosis treatment, the more obvious the results. Given poor maternal and fetal outcomes with untreated active TB disease, the benefits of treatment outweigh the potential risks from the medications[6]. In terms of drugs, a growing number of reports have shown that first-line anti-TB drugs including rifampicin, isoniazid, pyrazinamide and ethambutol have no adverse effects on fetuses at conventional doses[22, 23]. All first-line drugs can be used during pregnancy, except for streptomycin, which has toxic effects on the fetus[24]. The patient was

in the second or third trimester of pregnancy, and showed no special discomfort after anti-tuberculosis treatment with INH, RFP, EMB and PZA. The fetus showed no abnormality after reexamination, and labor induction was not performed. The lesion absorption improved and the patient was discharged from hospital. Most scholars believe that tuberculosis is not an indication of termination of pregnancy, but termination of pregnancy should be recommended under the following circumstances. (1) Active pulmonary tuberculosis in early pregnancy needs timely anti-tuberculosis treatment, considering the unavoidable adverse effects of drugs on the fetus. (2) Severe pulmonary tuberculosis with decreased lung function, unable to tolerate continued pregnancy and delivery. (3) AIDS patients develop tuberculosis during pregnancy. (4) The pregnancy cannot be continued with other systemic diseases.

Conclusions

In short, the interaction between tuberculosis and pregnancy is like a double-edged sword. On the one hand, pregnancy affects the progress of tuberculosis, and on the other hand, tuberculosis affects pregnancy and newborn. Early detection, early diagnosis and early treatment are the key to determine the prognosis. For patients with atypical clinical symptoms and under the influence of COVID-19 epidemic, it is recommended to conduct chest imaging examination and follow the principle of the lowest dose as possible. There is no obvious harm to the fetus caused by the use of X-rays and CT in land acquisition during pregnancy. At the same time, raising doctors' awareness on tuberculosis is fundamental, and early diagnosis and standardized treatment are the key to improve the outcome of pregnancy.

Declarations

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Authors' contributions

Not applicable.

Availability of data and materials

All the relevant data is included in the case report. Reasonable request for any additional data can contact with the corresponding author.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying figures or images. A copy of the written consent is available for review..

Competing interests

The authors have no conflicts of interest.

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Figures

Graph 1

Figure 1

The initial diagnosis was "acute respiratory failure, severe pneumonia, 28 weeks of gestation".

Graph 2

Figure 2

The patient was discharged with medicine on January 29. And on March 10, the culture results of *Mycobacterium tuberculosis* were positive and sensitive to first-line anti-tuberculosis drugs.