Infection and Drug Resistance Dovepress

Open Access Full Text Article

CASE REPORT

Tuberculosis Caused by Isoniazid-Resistant Strain Was Transmitted from a Woman Undergoing IVFET to Her Fetus by Intrauterine: A Case Report

Sinian Li[1,*], Jin Wang[1,*], Hong Yu[2], Hua Huang[3], Shui Hua Lu[1], Xiaomin Wang[4], Mutong Fang[1]

[1]Pulmonary Diseases Department, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, People's Republic of China; [2]Pathology Department, The Third People's Hospital of Shenzhen, Shenzhen, People's Republic of China; [3]Imaging Department, The Third People's Hospital of Shenzhen, Shenzhen, People's Republic of China; [4]National Clinical Research Center for Infectious Disease (Shenzhen), Shenzhen, 518112, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mutong Fang; Xiaomin Wang, Email 1049179464@qq.com; WXM_ZMU@163.com

Background: Tuberculosis (TB) among women and infants during the perinatal period is not rare, particularly in countries with a high TB burden. And the risk would increase significantly following in vitro fertilization-embryo transfer (IVFET). Worse still, TB in this stage is apt to develop into severe forms in women and neonates, such as disseminated TB or tuberculous meningitis (TBM). On the other hand, severe adverse effects (SAEs) of anti-tuberculosis (ATB) agents in neonates were common but difficult to diagnose early and manage well.

Case Presentation: A 29-year-old mother receiving IVFET and her 3-month-old infant were diagnosed with disseminated tuberculosis and cranial tuberculoma on Dec 29, 2024, based on typical imaging features and bacteriological evidence. Intrauterine transmission of an isoniazid-resistant strain was confirmed through whole-genome sequencing (WGS) analysis and epidemiological investigation. ATB therapy and adjuvant treatment were initiated as soon as the confirmation of TB. Favorable therapeutic effects were achieved for them, and their condition stayed well until the last visit on Nov 19, 2024. However, the infant's ATB therapy had to be adjusted several times because of severe drug-induced liver injury (DILI) and lactic acidosis caused by ATB drugs during the treatment. In the end, he also obtained satisfactory outcomes.

Conclusion: Clinicians should stay alert for TB in pregnant women who underwent IVFET as well as their neonates. Our case report may improve clinicians' awareness and ability to manage severe TB during the perinatal period.

Keywords: cranial tuberculomas, isoniazid-resistant, IVFET, genital TB, congenital TB, WGS analysis

Background

In 2023, an estimated 10.8 million people fell ill with TB worldwide, and a total of 1.25 million people died from it. TB has returned to being the world's leading cause of death from a single infectious agent after the age of coronavirus disease (COVID-19).[1] The burden of TB during pregnancy is not very clear, but it is estimated at 216,500 cases per year in the world. Although the effect of pregnancy on TB risk stayed uncertain, studies indicated that pregnancy was associated with a 2 to 3-fold increase in risk of TB. Congenital TB was rare but extremely serious.[2] IVFET is an important assisted reproductive technology (ART) for treating women's infertility. However, tuberculosis (TB) among women receiving IVFET has been frequent in TB-high-burden countries. Studies showed that receiving IVFET was associated with much worse maternal and perinatal outcomes when compared to natural pregnancy, including maternal criticality (21.4% vs 2.0%), miliary TB (89.3% vs 13.5%), TB meningitis (32.1% vs 7.7%), and perinatal mortality (64.3% vs 28.8%).[3,4] Therefore, clinicians must pay close attention to the group. Herein, we reported a rare case of

Received: 2 July 2024
Accepted: 2 December 2024
Published: 7 December 2024

a mother undergoing IVFET who developed disseminated TB and cranial tuberculoma caused by an isoniazid-resistant strain. TB was transmitted to her fetus through intrauterine. They recovered well following effective anti-tuberculosis (ATB) treatment and successful management of SAEs. This case report may help improve clinicians' awareness and ability to manage severe TB during the perinatal period, especially for neonates.

Case Presentation

Maternal

A 29-year-old woman underwent IVFET in Mar 2023 for infertility. She gave birth to a male infant via a cesarean section on Oct 16, 2023. The infant was diagnosed with pulmonary tuberculosis (PTB) on Dec 29, 2023. However, the woman presented without cough, fever, headache, stiff neck, etc. Chest computed tomography (CT) revealed diffuse miliary nodular in both lungs and moderate pericardial effusion on Dec 29, 2023 (Figure 1A). Magnetic resonance imaging (MRI) showed a lesion in the left pontine brain with noticeable circular enhancement and peripheral edema on Jan 4, 2024 (Figure 1B and C). The pressure and routine biochemical assays of cerebrospinal fluid (CSF) were normal, but the results of the etiological assay were negative. GeneXpert *MTB*/RIF (Xpert) in Bronchoalveolar lavage fluid (BALF) was positive (very low) without rifampicin resistance. Accordingly, she was diagnosed with miliary TB complicated by a cranial tuberculoma. On Jan 3, 2024, an ATB regimen comprising isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) was initiated. On January 6, 2024, Linezolid (LZD) was added to strengthen the ATB treatment, and dexamethasone was administered for its anti-inflammatory effects. On 25 Feb 2024, INH was replaced with levofloxacin (Lfx) based on the infant drug susceptibility test (DST) and WHO guidelines. On Mar 6, 2024. The DST of *mycobacterium tuberculosis* (*MTB)* isolated from her BALF verified resistance to INH. She recovered well without any SAEs. Lzd was discontinued on Apr 20, 2024. Chest CT (Figure 1D) and cranial MRI (Figure 1E and F) showed the tuberculoma and edema zone around it was nearly unseen on Jul 19, 2024. The current treatment was expected to be discontinued on Dec 31, 2024.

Infant

Male, born by cesarean section without inoculation with Bacillus Calmette Guerin vaccine (BCG) on Oct 4, 2023 (29W +5d). He was kept in an incubator and received artificial feeding immediately at birth. He presented without cough, fever, or dyspnea when born. On Oct 28, necrotizing enterocolitis was diagnosed based on abdominal distension, bloody stool, and poor peripheral circulation. A surgical resection of the ileocecal colon was performed on Dec 15 when conservative medical treatment did not work. The pathology of the ileocecal colon was consistent with the inflammatory changes. On Nov 8, his left inguinal lymph node was found to be swollen and ruptured. Pathological examination revealed necrotizing granulomatous inflammation. Acid-fast and fluorescein staining were positive (Figure 1G and H). Xpert was positive (low) without RIF resistance in pus from the left inguinal lymph node, gastric juice, and stool. Chest CT revealed a mass in the right lower lung and multiple nodules in both lungs (Figure 1I). Enhancing cranial MRI indicated a space-occupying lesion with ring enhancement and peripheral edema in the left brainstem (Figure 1J and K). Lumbar puncture was not performed for fear of causing a cerebral hernia, according to consultation from a neurologist and neonatologist. The liver, kidney, and coagulation functions were normal. Accordingly, the infant was diagnosed with disseminated TB and cranial tuberculoma on Dec 28, 2023 (about 3 months after birth). An ATB regimen comprising INH (10 mg/kg), RIF (15 mg/kg), and PZA (40 mg/kg) was initiated on Dec 29, 2023. However, his food intake soon decreased, and he became weak. His skin and eyes became yellow, and his urine turned dark without pale stools or pruritus. Blood biochemistry test showed ALT: 198 U/L, AST: 290 U/L, TBIL: 69.1 umol/L, DBIL: 63.8 umol/L. PT: 21.1 S, APTT: 61.2 S, INR: 1.88 on Jan 4, 2024. The original anti-tuberculosis regimen was immediately interrupted and switched to Lzd (10 mg/kg, q8h) and levofloxacin (Lfx, 15 mg/kg, qd) for anti-tuberculosis. Dexamethasone was administered as an anti-inflammatory agent. Other measures included glycyrrhizin for relieving inflammation of hepatocytes, vitamin K1, fresh plasma for the correction of coagulopathy, and nutritional support. His condition gradually improved, food intake increased, and jaundice disappeared. Liver and coagulation function normalized gradually. On Jan 18, 2024, INH was added to intensify the ATB treatment. Dexamethasone was replaced with methylprednisolone tablets, which were tapered

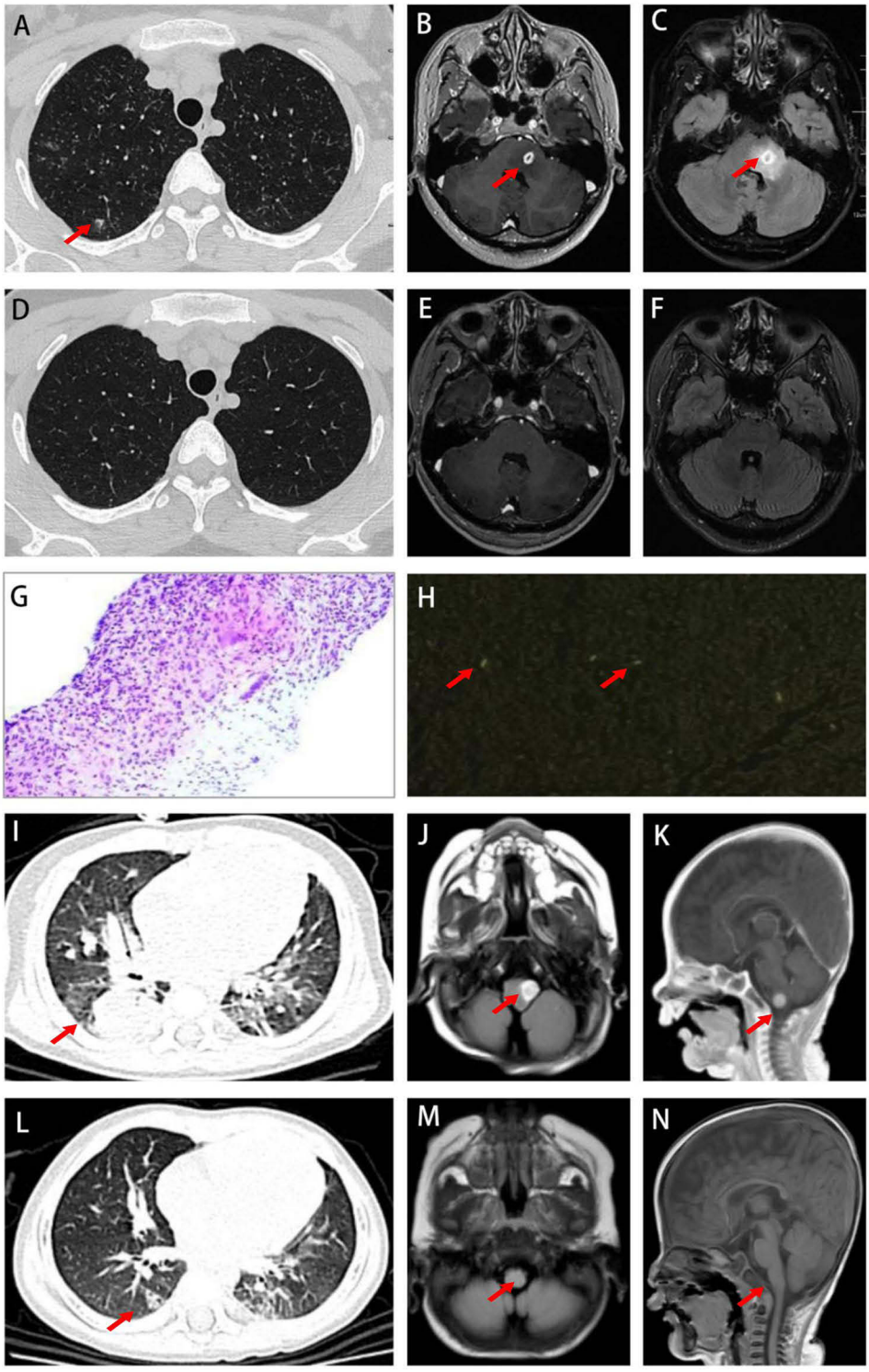

Figure 1 The radiological and pathological data. On Dec 29, 2023, Mother's chest CT showed diffuse miliary nodular (red arrow) in both lungs (**A**). Enhancing MRI revealed a lesion with circular enhancement (red arrow) and peripheral edema in the left pontine brain (**B** and **C**). On Jul 19, 2024, Chest CT revealed that the miliary nodular had almost disappeared (**D**), and MRI showed the tuberculoma and edema zone around it were nearly unseen (**E** and **F**). The pathology of infant's lymph node showed necrotizing granulomatous inflammation (**G**). The acid-fast staining and fluorescent staining (red arrow) were positive (**H**) on Nov 8, 2023. On Jan 1, 2024, the infant's chest CT showed a mass in the right lower lung (red arrow) as well as multiple nodules in both lungs (**I**). On Jan 1, 2024, an enhancing cranial MRI indicated a space-occupying lesion with ring enhancement (red arrow) on the left brainstem (**J** and **K**). On Jul 19, 2024. The chest CT showed that the mass shrank significantly (red arrow) and most nodules were absorbed in both lungs (**L**). On 5 Mar 2024, the MRI displayed no lesion (red arrow) existed in the brain stem (**M** and **N**).

off and ceased. On Feb 16, 2024, DST of *MTB* isolated from sputum cultures indicated resistance to INH, cycloserine (Cs), ethionamide (Eto), and p-aminosalicylic acid (Pas) and susceptible to RIF, Lfx, and EMB. Therefore, INH was replaced with RIF, which was gradually increased to 15 mg/kg/d from 5 mg/kg/d for safety. EBM was administered to intensify the regimen. Liver function and other AEs were closely monitored. On Mar 1, 2024, a blood test showed lactate level elevated to 8.6 mmol/L (reference range 1.0–3.3 mmol/L) and PH value lowered to 7.27 in artery blood. But his condition stayed well. Lzd was discontinued on the same day on suspicion of lactic acidosis caused by it. Then, his blood lactate level lowered, and his PH value recovered normally. On Jul 6, 2024, CT showed the lesions in both lungs were nearly absorbed completely (Figure 1L). On Jul 8, 2024, an MRI revealed the left brainstem lesion and the edema zone around it had almost disappeared (Figure 1M and N). His final treatment regimen, comprising RIF, Lfx, and EMB, was well tolerated until the revised manuscript was submitted. The total treatment course was expected to be 18 months.

WGS Analysis

Genomic DNA was extracted from MTB strains isolated from mothers and infants. Genomic DNA samples were sequenced at a depth of >200× and coverage of more than 99%. Only three SNPs differed between the genomes of these two strains, which were analyzed using PANPASCO software. Drug resistance prediction based on mutations showed that both the strains were resistant to isoniazid and streptomycin. In addition, both strains had the same drug resistance mutations: C-15T in fabG1 and G102del in gids.

Discussion

IVFET was identified as a risk factor for military TB and TBM compared with natural pregnancy for women.[4] Firstly, genital TB (GTB) involving the fallopian tubes, ovaries, pelvic peritoneum, and endometrium might have existed before IVFET. Previous studies have shown that GTB was responsible for infertility in most women in TB high-load countries.[5] Secondly, T-cell immunity against TB was compromised in the third trimester by the sharp elevation of hormone levels and intervention medications related to IVFET.[6] Finally, delayed diagnosis seems very common in pregnant women due to the atypical presentation and unavailability of X-ray examinations. It seemed very rare for the woman not to present with any symptoms even though she had developed miliary TB and cranial tuberculoma. Therefore, clinicians should consider GTB a common cause of infertility in women. Before IVFET, TB needed to be excluded by necessary measures. Furthermore, TB should be considered to be a significant complication of IVFET for mothers and neonates.

Tuberculoma is a rare form of central nervous system tuberculosis (CNS-TB). It can only be confirmed by brain biopsy or autopsy. Pure tuberculoma was uninvolved in the meningeal, leading to a normal CSF assay. Enhanced MRI can reveal valuable features of tuberculomas, including ring enhancement of the lesion and peripheral edema. The lesion shrank after ATB treatment. These features helped differentiate tuberculoma from a tumor or cerebral cysticercosis.[7,8] The mother and her infant's MRI were consistent with the above features of tuberculoma. As a result, a clinical diagnosis of tuberculoma was established with the coexistence of PTB. Unprecedentedly, solitary tuberculomas were located in or near their left brainstem by coincidence.

Infant's TB should be transmitted from the mother through intrauterine rather than by respiratory tract. The reasons include the following aspects. Firstly, he was separated from her mother at birth. Secondly, PTB was ruled out for other close contacts. More importantly, the genomes of the two strains were highly homologous according to WGS analysis. Both the strains had the same drug resistance mutations of INH and Streptomycin. This indicated the recent transmission of the primary resistant strain from mother to infant. WGS has been verified to be the most rapid and accurate method for identifying the origin and resistance profiles of *MTB*.

TB was prone to progress to a severe form in premature infants because of their immature immunity, especially in case of delayed diagnosis.[9] It had taken 2 months to confirm TB for the infant. Severe DILI occurred soon after ATB treatment, resulting in the withdrawal of treatment. However, TB was controlled following the application of Lfx and Lzd. Lfx and Lzd had vigorous early bactericidal activity against *MTB* strains and excellent blood–brain barrier (BBB) permeability. Another advantage was their milder hepatotoxicity. However, only two medications seemed too weak to control the infant's severe TB and might have induced further resistance. Therefore, RIF was added to strengthen the ATB activity. RIF remained the cornerstone of TBM treatment, as it could penetrate the BBB effectively, especially in

infants whose BBB was not intact.[10] The infant's liver function remained normal after the application of RIF, indicating that PZA was responsible for previous severe DILI. LILA caused by Lzd was rare but may be lethal SAE. Withdrawal of Lzd was the critical measure. However, some severe cases may need the treatment of continuous venovenous hemodiafiltration. The occurrence of severe DILI and LILA supported the necessity to monitor the adverse reactions of ATB drugs, especially for infants who were not able to express discomfort.

Conclusion

Our case report indicates that it is necessary to perform TB screening before IVFET and to identify TB as early as possible during the perinatal period. The management of SAEs remains as essential as their therapeutic effects in the treatment of severe congenital TB. MDT is indispensable for achieving favorable outcomes in infants.

Abbreviations

TB, tuberculosis; MTB, Mycobacterium tuberculosis; IVFET, in vitro fertilization embryo transfer; TBM, tuberculous meningitis; WGS, whole-genome sequencing; DST, drug susceptibility test; ATB, anti-tuberculosis; DILI, drug-induced liver injury; SAEs, severe adverse effects; PTB, pulmonary tuberculosis; CT, computed tomography; MRI, Magnetic resonance imaging; CSF, cerebrospinal fluid; Xpert, GeneXpert MTB/RIF; INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; LILA, Linezolid-induced lactic acidosis; LZD, linezolid; Lfx, levofloxacin; CS, cycloserine; Eto, ethionamide; BALF, bronchoalveolar lavage fluid; BCG, Bacillus Calmette Guerin vaccine; CNS-TB, central nervous system tuberculosis; GTB, Genital TB; BBB, blood–brain barrier.

Data Sharing Statement

The main data are provided in the manuscript, and the rest are available from the corresponding author Mutong Fang upon reasonable request.

Ethics Approval

This study was approved by the Ethics Committee of Shenzhen Third People's Hospital (No. 2022-096-02) and complied with the Declaration of Helsinki. The committee also permitted the publication of the case detail.

Consent for Publication

The patient (the woman and her husband) provided written informed consent to publish this case report.

Acknowledgments

We sincerely thank the clinicians who managed this infant at Shenzhen Children's Hospital.

Author Contributions

Sinian Li and Jin Wang contributed equally as co-first authors. All the authors have read and approved the final manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by: Shenzhen Third People's Hospital Project (No. G2022058); The Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (No. SZGSP010); Shenzhen Medical Research Fund (No: C2405002) from Shenzhen Medical Academy of Research and Translation (SMART). The funding organizations had no role in the design of the study; collection, analysis, or interpretation of the data; or in writing the manuscript.

Disclosure

The authors declare that they have no competing interests.

References

1. World Health Organization. Global tuberculosis report 2024. Geneva: Global Report; 2024. Available from: https://www.who.int/publications/i/item/9789240101531. Accessed December 4, 2024.
2. Snow KJ, Bekker A, Huang GK, Graham SM. Tuberculosis in pregnant women and neonates: a meta-review of current evidence. *Paediatr Respir Rev*. 2020;36:27–32.
3. Xia L, Mijiti P, Liu X-H, et al. Association of in vitro fertilization with maternal and perinatal outcomes among pregnant women with active tuberculosis: a retrospective hospital-based cohort study. *Front Public Health*. 2022;10:1021998. doi:10.3389/fpubh.2022.1021998
4. Wei JL, Zhang L, Xu Y-L, et al. Case-controlled study of tuberculosis in in-vitro fertilisation-embryo transfer and natural pregnancy. *BMC Pregnancy Childbirth*. 2024;24(1):77. doi:10.1186/s12884-024-06260-1
5. Tal R, Lawal T, Granger E, et al. Genital tuberculosis screening at an academic fertility center in the United States. *Am J Obstet Gynecol*. 2020;223(5):737.e1–737.e10. doi:10.1016/j.ajog.2020.05.045
6. Saha A, Escuduero J, Layouni T, et al. Mycobacterium tuberculosis-specific T-cell responses are impaired during late pregnancy with elevated biomarkers of tuberculosis risk postpartum. *J Infect Dis*. 2022;225:1663–1674. doi:10.1093/infdis/jiab614
7. Gothi R. Consider tuberculoma and cysticercosis in the differential diagnosis of brain tumour in tropical countries. *BMJ*. 2013;347:f6604. doi:10.1136/bmj.f6604
8. Akhaddar A, Boucetta M. Images in clinical medicine. Multiple intracranial tuberculomas. *N Engl J Med*. 2011;365(16):1527. doi:10.1056/NEJMicm1103165
9. Zhang F, Zhang XF, Zhou HY. Clinical characteristics in 26 children with congenital tuberculosis in Central Southern China: a retrospective study. *Paediatr Int Child Health*. 2022;42(3–4):127–132. doi:10.1080/20469047.2023.2246006
10. Wasserman S, Davis A, Wilkinson RJ, et al. Key considerations in the pharmacotherapy of tuberculous meningitis. *Expert Opin Pharmacother*. 2019;20(15):1791–1795. doi:10.1080/14656566.2019.1638912