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Case Report
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Miliary Tuberculosis with *Mycobacterium bovis*: A Silent Threat for *In Vitro* Fertilization Pregnancies

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Abstract

Miliary tuberculosis, a disseminated form of tuberculosis, is less common in developed countries. Case reports outside the United States have reported miliary tuberculosis in pregnancies with *in vitro* fertilization. We present a clinical scenario involving *in vitro* fertilization pregnancy that rapidly progressed from latent tuberculosis to miliary tuberculosis based on imaging. We also explore existing literature on miliary tuberculosis in pregnancy and *in vitro* fertilization conceptions. The combined effects of immune modulation of pregnancy and *in vitro* fertilization may increase risk of tuberculosis progression. To optimize maternal health, we suggest screening for tuberculosis prior to pregnancy with assisted reproductive technology.

Keywords: Miliary tuberculosis; Disseminated tuberculosis; *Mycobacterium bovis*; IVF; Infection in pregnancy

Introduction

Pregnancy is a unique time of physiologic immune modulation that supports the development of the pregnancy. However, this immune modulation may increase the risk of other infectious processes. Pregnancy provides an opportunity to screen for various infectious diseases to promote overall wellbeing of the pregnant person and developing pregnancy, such as Tuberculosis (TB). Pregnant women are recommended to be screened for TB since this can affect the pregnant person, pregnancy, and neonate; this is increasingly important with growing frequency of foreign-born pregnant persons [1,2]. Screening during pregnancy involves assessing recent exposure to people infected with TB or medical conditions present that further weakens immune response in pregnancy [1]. This screening process identified at risk persons to enable treatment based on disease severity, even during pregnancy.

Case Presentation

A 36-year-old G2 P0010 presented at 12 weeks gestation for prenatal care with pregnancy by *In Vitro* Fertilization (IVF). Her history was significant for migration from a farm in Mexico 20 years prior. She appeared well and routine labs were only remarkable for positive TB screening by interferon gamma release assay with plan for chest X-ray in the second trimester. At 19 weeks, the patient presented to the emergency department with progressively worsened headache over a month and one week of blurred vision. She later admitted to mild cough for two months. Her imaging had significant findings: 1) bilateral hemisphere lesions with associated vasogenic edema on Magnetic Resonance Imaging (MRI) (Figure 1A) and 2) bilateral ground glass opacifications on chest X-ray. Because of her cerebral edema, lumbar puncture was deemed unsafe due to risk of herniation. An extensive diagnostic evaluation was initiated with high suspicion for infectious etiology despite no recent exposure or history was elicited.

Throughout the admission, the patient continued to experience headaches and an ophthalmologic exam noted papilledema. Computed Tomography (CT) of head noted severe edema in bilateral cerebral hemispheres, brainstem and bilateral cerebellum with mass effect on the ventricles. MRI of total spine revealed a lesion at T12 level along with edema from T10 to conus medullaris resulting in cord expansion (Figure 1B). A CT of the chest revealed innumerable micronodules bilaterally. The patient was empirically started on dexamethasone, rifampicin, isoniazid, pyrazinamide,

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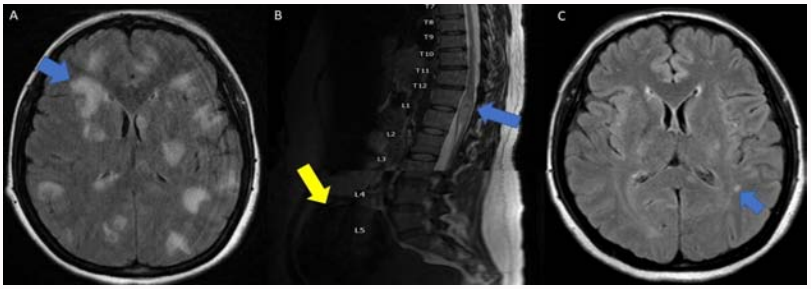

Figure 1: Images from patient described in clinical scenario.
A. MRI brain without contrast in T2 flair at time of diagnosis with multiple bilateral tuberculomas as well as vasogenic edema (blue arrow pointing to representative lesion).
B. MRI spine without contrast in T2 flair at time of diagnosis with target lesion at T12 level and surrounding edema (blue arrow). Lower portion from T1 Scout of MRI and gravid uterus (yellow arrow).
C. MRI brain without contract in T2 flair at time of delivery with resolution of edema as well as decreased lesions (blue arrow pointing to area of residual lesion).

and ethambutol secondary to high suspicion of miliary TB. All sputum smears were negative with only one culture positive for *Mycobacterium bovis*. With initiation of treatment, her neurologic symptoms improved, and subsequent MRI head showed interval decrease in brain edema. She continued outpatient treatment with the department of health throughout pregnancy.

At 31 weeks, she was diagnosed with cholestasis of pregnancy based on symptoms, bile acids >150 μmol/L, and transaminitis; this was deemed unrelated to rifampin and isoniazid use since prior labs were within normal limits. She delivered at 36 weeks with postpartum normalization of liver function tests. Repeat brain imaging after delivery showed a decrease in most brain lesions (Figure 1C). The neonate underwent evaluation without signs of TB or adverse effects of medication exposure. The patient continued postpartum treatment and follow up care.

Discussion

Pregnancy is characterized by immune modulation of T-cell immunity which TB may be able to exploit. The progression from latent to disseminated disease can occur rapidly, within days to weeks, due to immune escape mechanisms [3]. Diagnosis can be particularly challenging in patients with mild or atypical symptoms. Tuberculosis is generally caused by the organism *Mycobacterium tuberculosis* with 4 other types, including *M. bovis*; the other identified subtypes are unlikely in humans unless co-infection with HIV is present [4]. Miliary TB often has low bacterial burden in the intra-alveolar space; this results in low sensitivity of sputum smears and delays in diagnosis [3,5]. In our case, we also experienced difficulty in organism isolation necessitating multiple cultures to confirm the suspected diagnosis.

Our patient presented with a common symptom: Headache. Neurologic and meningeal TB can present with benign symptoms of headache, visual changes, emesis, and/or dizziness [4]. While the lung used to be the most common location of TB, pregnant individuals may be more prone to extra-pulmonary presentation [2]. CT and MRI can be utilized, with appropriate counseling, to determine the extent of TB. In our case, she rapidly transitioned from evaluation for latent TB to miliary TB diagnosis based on her imaging. Miliary TB can have subtle manifestations and severity may not correlate with radiologic findings due to broad lymphohematogenous dissemination; thus, requiring multi-drug prolonged treatment strategy [3,5].

Following the diagnosis of miliary TB, there are ongoing risks to the pregnancy even with treatment. Maternal implications of miliary TB include increased risk for chorioamnionitis, threatened preterm labor, postpartum anemia, blood transfusion, respiratory compromise, and mortality [2]. Additionally, there is also increased risk of congenital anomalies and congenital infection, although data on preterm delivery, low birth weight, and small for gestational age are inconsistent [2,4]. The potential risks of TB depend on several factors including: Location of TB, severity of disease, HIV co-infection, gestational age at diagnosis, treatment initiation, and treatment compliance [4].

In light of our patient's diagnosis, we further considered the role of IVF conception in miliary TB diagnosis. A cohort in China involving 23 patients with miliary TB compared conception method revealing higher frequency of symptoms in the first trimester among IVF conceptions [5]. While cases of miliary TB in IVF conceptions have been reported, the exact mechanism remained unclear; however exogenous hormones used in IVF may further suppress T cell immunity [5]. There is likely benefit from preconception TB screening in these patients [6].

In conclusion, our review focused on the diagnosis of miliary TB in an IVF pregnancy. While our patient exhibited symptoms that aided in her diagnosis, the overall morbidity remained low for the patient and fetus due to timely diagnosis, treatment, and close monitoring throughout pregnancy. However, identifying TB prior to pregnancy could have presented an opportunity for treatment and potentially reduced morbidity further. For patients undergoing or planning IVF conception, there is likely benefit to screening and treating for TB prior to implantation to optimize maternal health and prevent disease progression during pregnancy.

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