Diagnosing Common Deadly Infections in the Era of COVID-19
A Case Report

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Abstract: The COVID-19 pandemic has challenged clinicians to recognize COVID-19 as one of the diagnostic explanation for common presentations, including fever, cough, and shortness of breath. Latent tuberculosis is responsible for 80% of active tuberculosis cases in the United States, and presentation can vary from asymptomatic to disseminated disease. This potential diagnosis should be thoroughly investigated in foreign-born patients in US hospitals, regardless of travel history and presenting symptoms. We report a patient diagnosed with postpartum disseminated tuberculosis with hematogenous spread to the fetus.

Key Words: disseminated tuberculosis in pregnancy, latent tuberculosis, reactivation of latent tuberculosis, tuberculosis in pregnancy

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Most active tuberculosis infection (ATBI) cases in the United States are attributed to reactivation of latent tuberculosis infection (LTBI). Approximately 2 billion people are infected with LTBI (WHO2009) worldwide. The United States is considered to be a low tuberculosis (TB) prevalence country; New York City (NYC) has consistently been a high-risk area for TB.[1,2] Prevalence of LTBI in the US general population is up to 10 times higher among foreign-born Americans,[3] including pregnant women,[4] regardless of HIV status. Reactivation of LTBI is certainly more common in HIV-positive women,[5,6] and they are more likely to develop ATBI with a positive Interferon Gamma Release Assay test.

Immunosuppression contributes significantly to the development of ATBI. Centers for Disease Control and Prevention guidelines recommend screening for LTBI in patients requiring long-term immunosuppressive therapy.[7] Corticosteroid treatment and pregnancy are both known to cause immunosuppression. Centers for Disease Control and Prevention guidelines indicate that 15 mg of prednisolone taken for 2 to 4 weeks might increase the chances of ATBI, given it can suppress tuberculin reactivity. In the United States, Centers for Disease Control and Prevention recommends LTBI screening only for high-risk women, and pregnancy by itself is not considered a high-risk state, neither does short-term low-dose steroids use.

We present a case of a pregnant HIV-negative woman, diagnosed with disseminated TB.

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CASE DESCRIPTION SUMMARY

A 33-year-old, 29 weeks' pregnant woman from Haiti with sickle cell trait presented with nonproductive cough for 3 days. She did not have fever, chills, chest pain, night sweats, hemoptysis, weight loss, urinary, gastrointestinal, or neurologic symptoms. There were no sick contacts and no known exposure to anyone with COVID-19. She had traveled to Haiti in January 2020. Prenatal care started 4 months before presentation, with all the appropriate screening tests negative, including HIV.

The initial physical examination showed a temperature of 38.1°C, heart rate of 115 beats/min, respiratory rate of 19, blood pressure of 117/56, and oxygen saturation of 96% on room air. Laboratory evaluation was significant for elevated alkaline phosphatase of 133 IU/L, aspartate aminotransferase of 46 IU/L, alanine aminotransferase of 63 IU/L, and absolute lymphocyte count of 0.9 (N = 1.2–3.4 K/UL). Urinalysis was unremarkable. SARS-CoV-2 reverse transcription polymerase chain reaction (PCR) was negative. Hepatitis screen showed hepatitis B surface antibodies and hepatitis A immunoglobulin G present. Three samples of induced sputum for acid-fast bacillus (AFB) smear were negative. Computed tomography angiogram of the chest was negative for pulmonary emboli and showed scattered opacities in both lungs with punctate calcified granuloma in the right lower lobe.

The patient developed hypoxia on hospital day (HD) 1 and was treated with ceftriaxone 1 g, intravenously, daily and azithromycin 500 mg daily for possible community-acquired pneumonia, and dexamethasone 6 mg, orally, daily for 5 days for hypoxia secondary to possible COVID-19 illness. Antibiotic treatment was changed to vancomycin and piperacillin/tazobactam on HD 7 because of persistent fever.

On HD 23, the respiratory status worsened, and the patient was transferred to the medical intensive care unit. Angiotensin-converting enzyme was elevated (106 U/L), and vitamin D-1.25 was decreased (143 ng/mL). Methylprednisolone 2 mg/kg was started for possible sarcoidosis, with a noticeable improvement in symptoms on the next day. Patient underwent induction of labor to safely perform bronchoscopy but underwent urgent C-section HD 28 due to maternal hypoxia. The respiratory symptoms improved soon thereafter. On postoperative day (POD) 2 (HD 30), the patient complained of headache. The temperature was 39.1°C, and vancomycin and piperacillin/tazobactam were restarted.

On POD 8 (HD 36), the patient became minimally responsive to commands. Computed tomography angiogram of the head showed nonobstructive hydrocephalus, with posterior bilateral parietal hypodensities, concerning for diffuse extensive vasoconstriction (posterior reversible encephalopathy syndrome [PRES] and reversible cerebral vasoconstriction syndrome [RCVS]), or possible vasculitis. The dose of methylprednisolone was increased for possible neurosarcoidosis. Acyclovir was added for possible herpes simplex virus encephalitis.

The patient was transferred to Maimonides Medical Center, where head magnetic resonance imaging showed multiple ring enhancing

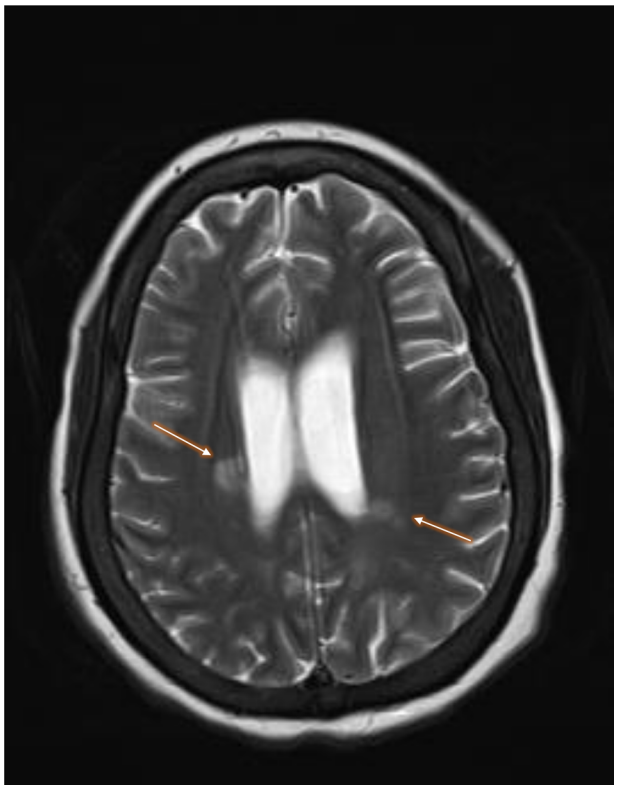

FIGURE 1. T2-weighted magnetic resonance imaging of the brain showing enhanced lesions (arrows) and enlarged lateral ventricles.

lesions with restricted diffusion and hydrocephalus (Fig. 1), which required external ventricular drain placement. Cerebrospinal fluid analysis showed 370 leukocytes per cubic millimeter (90% polymorphonuclear cells), proteins 172 mg/dL, glucose 23 mg/dL (with simultaneous serum glucose of 209 mg/dL), histiocytes, and lactate dehydrogenase 393 U/L. Cerebrospinal fluid PCR detected cytomegalovirus (CMV), and blood CMV PCR was 439 IU/mL. Funduscopic evaluation was normal. Cerebrospinal fluid AFB smear revealed numerous acid-fast microorganisms, and mycobacterium tuberculosis (MTB)-PCR was positive on POD 9 (HD 37). Pathology of the placenta showed multiple necrotizing granulomas and microabscesses, which stained positive for AFB. Acid-fast bacillus smear and initial cultures were negative. Third sputum sample collected 3 weeks after admission was positive a month later. Upon reevaluation of patient's past medical records, it was discovered that she had a preconception visit to an outside clinic, significant for positive IGRA, but negative chest x-ray (CXR). The follow-up status and recommendations for treatment of possible LTBI at the time were unknown.

Treatment with rifampin, ethambutol, isoniazid, pyrazinamide, pyridoxine, and linezolid for disseminated TB, in addition to ganciclovir for reactivated CMV, was started. The patient's hospital course was complicated by recurrent strokes and respiratory failure, eventually requiring tracheostomy placement. The patient died 20 days after transfer, which occurred on POD 29 (HD 57).

DISCUSSION

Disseminated TB is a life-threatening condition, posing a challenging diagnosis. Maternal mortality from this condition has been reported to be as high as 38%.[8] We present a case of TB reactivation in a pregnant woman, with dissemination, which ultimately resulted in her death. To our knowledge, there are only a few reports of disseminated peripartum TB with hematogenous spread to fetus similar to our case referenced.[9] We postulate that high-dose steroids that she received for more than 10 days and postpartum immune reconstitution phenomenon played a significant role in the cascade of events.

The patient had several possible factors leading to the dissemination of TB. The patient remained undiagnosed for an extended period, delaying the initiation of ATBI treatment. Atypical presentation unclearly differentiated between COVID19 infection, hepatic changes due to pregnancy, TB, and sarcoidosis played a significant role in diagnostic delays. Since admission, she received 12 days of steroids with a cumulative dose of more than 700 mg before being diagnosed, which may have caused immunosuppression.[10–12]

Pregnancy is a state of relative immunosuppression, characterized by anti-inflammatory cellular responses that promote tolerance to fetal antigens, which would otherwise be viewed as a foreign entity. As these changes reverse as early as 24 hours postpartum, they can result in overt clinical manifestations of latent infections,[13] attributed to the immune reconstitution phenomenon.[8]

The diagnosis of disseminated TB can be quite challenging and is usually delayed. Several factors can contribute to delays in timely diagnosis.[14] Among them are ambiguity of the symptoms, mimicking physiological pregnancy changes and laboratory diagnostic tools such as sputum AFB smear and culture being time-consuming, having low sensitivity, and the inability to easily detect miliary changes on CXR.[15,16] The culture from the initial smear-negative sputum specimen in our patient did not grow AFB. Only the third sputum sample grew AFB a month after initial presentation. In patients with suspected disseminated TB, bronchoscopy can be an alternative with a combination of different diagnostic modalities (smear, culture, and histology), increasing the sensitivity to 84% to 92%.[16] Unfortunately, bronchoscopy was relatively contraindicated in this pregnant patient.

Finally, it is still uncertain whether guidelines should be reinforced to warrant treatment of LTBI to prevent transition to ATBI. Pregnancy represents a unique opportunity for LTBI screening, especially in women who recently immigrated; potentially being the first time they are introduced to the US health care system.[7,17] With the new WHO End TB Strategy, planning to eliminate TB by 2035, there has been increased recognition of the importance of addressing LTBI, with improved screening methods and treatment recommendations.[18] Management of LTBI is considered one of the core interventions for TB eradication. Treatment with isoniazid for 6 to 12 months could significantly reduce the reactivation risk. However, both the length of therapy and associated hepatotoxicity risk reduce the acceptance of recommended treatment by the patient. It is possible to defer treatment until 2 to 3 months postpartum, unless there is a high risk of progression to ATBI, such as HIV infection, and recent contact with TB. The patient in the presented case had a history of a positive IGRA, which most likely never received treatment.

The current standard regimen for treatment of LTBI is 9 months of daily isoniazid or 4 months of rifampin. Although the NY Department of Health recommends the treatment, it is not mandatory; only 62% of the patients were found to have accepted and completed treatment.[19]

In conclusion, NYC represents a unique area: despite being part of a low-burden TB country, NYC has a high prevalence of TB cases given the large foreign-born population and high travel rates. Despite the low prevalence in the United States, disseminated TB should always be considered in the differential diagnosis in patients presenting to NYC hospitals with ambiguous symptoms. It is also important to rule out TB before initiating high-dose steroids. Treatment recommendations for diagnosed LTBI should be reinforced especially in non-US born women of child-bearing age.

REFERENCES

1. Bennett DE, Courval JM, Onorato I, et al. Prevalence of tuberculosis infection in the United States population: the national health and nutrition examination survey, 1999-2000. *Am J Respir Crit Care Med*. 2008;177(3): 348–355.
2. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. *PLoS One*. 2015;10(11): e0140881.
3. Blum RN, Polish LB, Tapy JM, et al. Results of screening for tuberculosis in foreign-born persons applying for adjustment of immigration status. *Chest*. 1993;103(6):1670–1674.
4. Schwartz N, Wagner SA, Keeler SM, et al. Universal tuberculosis screening in pregnancy. *Am J Perinatol*. 2009;26(6):447–451.
5. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1–infected women and their children. *J Infect Dis*. 2010;202(12): 1826–1835.
6. Leroy V, Msellati P, Lepage P, et al. Four years of natural history of HIV-1 infection in african women: a prospective cohort study in Kigali (Rwanda), 1988–1993. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;9(4): 415–421.
7. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000;49(RR-6):1–51.
8. Cheng VC, Woo PC, Lau SK, et al. Peripartum tuberculosis as a form of immunorestitution disease. *Eur J Clin Microbiol Infect Dis*. 2003;22(5): 313–317.
9. Abramowsky CR, Gutman J, Hilinski JA. Mycobacterium tuberculosis Infection of the placenta: a study of the early (innate) inflammatory response in two cases. *Pediatr Dev Pathol*. 2012;15(2):132–136.
10. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. *Rheum Dis Clin North Am*. 2016;42(1):157–176, ix-x.
11. Patil S, Jadhav A. Short course of high-dose steroids for anaphylaxis caused flare up of tuberculosis: a case report. *J Transl Int Med*. 2019;7(1):39–42.
12. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30.
13. Singh N, Perfect JR. Immune reconstitution syndrome and exacerbation of infections after pregnancy. *Clin Infect Dis*. 2007;45(9):1192–1199.
14. Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. *J Family Community Med*. 2019;26(2): 83–91.
15. Mert A, Bilir M, Tabak F, et al. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology*. 2001;6(3):217–224.
16. Tritou I, Prassopoulos P, Daskalogiannaki M, et al. Miliary hepatic tuberculosis not associated with splenic or lung involvement. a case report. *Acta Radiol*. 2000;41(5):479–481.
17. Williams C. Global tuberculosis control: WHO Report 2011. *Aust N Z J Public Health*. 2012;36(5):497–498.
18. Matteelli A, Rendon A, Tiberi S, et al. Tuberculosis elimination where are we now. *European Respiratory Review*. 2018;27(148).
19. Alsdurf H, Hill PC, Matteelli A, et al. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16(11):1269–1278.