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Tuberculous Meningitis in an Immunocompetent Host: A Case Report

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Study Design A
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Statistical Analysis C
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Patient: Male, 57
Final Diagnosis: Tuberculous meningitis
Symptoms: Altered mental state • headache
Medication: —
Clinical Procedure: Lumbar puncture
Specialty: Infectious Diseases

Objective: Rare disease

Background: Tuberculous meningitis is very rare in the United States in immunocompetent hosts. Risk factors are similar to those of pulmonary tuberculosis, including poverty, malnutrition, overcrowding, a compromised immune system, and coming from an endemic area. Meningeal tuberculosis mortality and other outcomes have changed little over time despite effective therapies due to delay in diagnosis because of its rarity, variable presentation, and often indolent course.

Case Report: We describe a case of a 57-year-old male immigrant from Senegal with no significant past medical history and no previous history of tuberculosis or evidence of immune compromise. He presented to the hospital with headache and altered mental status and was subsequently diagnosed with tuberculous meningitis.

Conclusions: This is a rare case of tuberculous meningitis in an immunocompetent host, questioning the conventional view that tuberculous meningitis is a disease of immunocompromised individuals. It emphasizes the importance of maintaining a strong clinical suspicion of tuberculous meningitis even in an immunocompetent patient in a geographical area with low prevalence if the patient has risk factors. Missed or delayed diagnosis is commonly fatal.

MeSH Keywords: Immunocompetence • Rare Diseases • Tuberculosis, Meningeal

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Background

Tuberculous meningitis occurs when lymphohematogenous spread follows primary infection or late reactivation of tuberculosis (TB) [1]. Risk factors are similar to those of pulmonary TB, including poverty, malnutrition, overcrowding, a compromised immune system, and coming from an endemic area. There were a total of 9,421 cases of TB reported in the United States in 2014. A total of 66% of reported TB cases in the US occurred among foreign-born persons. The case rate among foreign-born persons was approximately 13 times higher than among United States born persons. The rate of TB amongst Blacks, Africans, or African Americans is 5.1 TB cases per 100,000 persons as compared to 0.6 TB cases per 100,000 persons amongst Whites in the United States. This case is noteworthy because tuberculous meningitis in an immunocompetent host in the United States is very rare. It accounted for only 1% of all cases of TB in the United States in 2014 (or about 100 cases), and that includes mostly immunocompromised individuals [2]. In Senegal, there were a total of 23,647 cases of TB notified in 2014 (population of Senegal approximately 14 million), with 1,653 of these cases being extrapulmonary [3]. The Baccille Calmette Guerin (BCG) vaccine is the only approved vaccination for TB. In 2015, the World Health Organization (WHO) reported an estimated 95% BCG coverage of the Senegalese population. Estimates of BCG coverage in the United States are not reported by the WHO as this vaccination is not routinely given in the United States due to the low prevalence of the disease and the fact that people who have had BCG vaccines will often have a false positive result to a TB skin test which makes it more difficult to establish whether someone has latent TB [4].

Although pulmonary TB in the United States has declined, the number of meningeal TB cases and mortality has changed little despite effective treatment regimens. This is because recognition of the disease is often delayed due to its rarity and initial indolent course, and also because initial clinical presentation can be highly variable. Unfortunately, clinical outcomes are greatly worsened when therapy is initiated at a later stage [5,6].

Case Report

A 57-year-old non-English speaking male immigrant from Senegal with no significant past medical history and no health hazards presented with three weeks of headache and altered mental status. Our interview with the patient on admission and in fact throughout most of his 11-day hospital stay was limited due to his altered mental status and the language barrier, since the patient only spoke Fulani and a little bit of French. He was able to tell us that he had been doing temporary odd jobs since he moved to this country and was living in an apartment with several other work-related acquaintances. He denied any previous history or family history of TB. He had no significant family or friends in the United States who knew him well enough to provide further collateral information. We later found out when the patient's mental status improved that he had received the BCG vaccine as a child in Senegal.

Initial vital signs were temperature of 35.8 degrees Celsius, heart rate of 75 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 142/54 mL of mercury. The patient appeared malnourished and dehydrated, but was in no acute distress. He was alert but appeared confused and was oriented only to person. He was only able to answer simple questions and follow simple commands. He had no nuchal rigidity. The rest of his neurological examination was also unremarkable. Lungs revealed normal breath sounds bilaterally. Heart and abdominal examinations were unremarkable.

Basic metabolic panel revealed a sodium level of 122 mm/L. However, despite sodium levels eventually improving to 133 mm/L with normal saline, the patient's confusion did not significantly improve. Complete blood count, liver function tests, thyroid stimulating hormone, and urinalysis were within normal limits. Computed tomography (CT) of the head revealed a small remote left internal capsule lacunar infarct, but no acute hemorrhages or mass effect. Lumbar puncture was performed with cerebrospinal fluid (CSF) results showing an elevated total nucleated cell count with relative neutrophil predominance, an elevated total protein level, and a reduced glucose level (Table 1). Chest x-ray on admission showed only minimal right basilar opacity.

The patient was empirically placed on vancomycin, ceftriaxone, and ampicillin until CSF bacterial culture results showed no growth, at which point the antibiotics were discontinued. There was high suspicion for either TB or histoplasmosis, as the patient had emigrated from a continent where TB is endemic and immigrated to a region of the United States where histoplasmosis is endemic. Serum quantiFERON TB Gold was negative. However, *Mycobacterium tuberculosis* complex polymerase chain reaction (MTB-PCR) was obtained from CSF and was positive. CSF acid fast bacilli (AFB) smear was negative, but the AFB culture eventually grew an organism that was DNA hybridization probe positive for *Mycobacterium tuberculosis* complex. Given the positive CSF MTB-PCR and AFB culture results, the patient was diagnosed with tuberculous meningitis.

All other CSF workup including evaluation for histoplasmosis and other fungal agents, viruses, and bacteria were negative. Given that many patients with tuberculous meningitis can also have extra-meningeal disease as well, the patient was evaluated for pulmonary TB despite the clinical suspicion being low since he had no respiratory symptoms. AFB sputum

Table 1. Lumbar puncture results.

Tube	CSF	Results	Reference range	Units of measurement
Tube 1	Color	Pale yellow	Colorless	N/A
Tube 1	Clarity	Clear	Clear	N/A
Tube 1	Total nucleated cells	464	0–5	cell count/microliter
Tube 1	Neutrophils	21	0–6	%
Tube 1	Lymphocytes	41	40–80	%
Tube 1	Monocytes	14	15–45	%
Tube 1	Macrophages	1	No reference range given	%
Tube 1	Other cells	7	No reference range given	%
Tube 1	Red blood cells	0	0–10	Cell count/microliter
Tube 2	Glucose	19	40–70	mg/dL
Tube 3	Total protein	462	15–45	mg/dL
Tube 4	Color	Pale yellow	Colorless	N/A
Tube 4	Clarity	Clear	Clear	N/A
Tube 4	Total nucleated cells	466	0–5	Cell count/microliter
Tube 4	Neutrophils	19	0–6	%
Tube 4	Lymphocytes	62	40–80	%
Tube 4	Monocytes	16	15–45	%
Tube 4	Macrophages	1	No reference range given	%
Tube 4	Other cells	2	No reference range given	%
Tube 4	Red blood cells	0	0–10	Cell count/microliter

smears and cultures were obtained. Three AFB sputum smears came back negative, and AFB sputum cultures were negative after six weeks of incubation. The patient was evaluated for immunocompromised conditions – he was negative for infection with human immunodeficiency virus (HIV), had a normal complete blood count as mentioned previously, did not have a history of serious or recurrent infections at any point in his life until now, was not on any immunosuppressive medications, and did not display any signs or symptoms of malignancy nor did his CSF cytology or flow cytometry show any evidence of malignancy.

The patient was started on anti-tuberculous treatment which included isoniazid 300 mg PO daily, levofloxacin 750 mg PO daily, pyrazinamide 1500 mg PO daily, and rifampin 600 mg PO daily. His headache and confusion improved over the course of the next few days. As he did not have any evidence of pulmonary TB, he was discharged after arranging coordinated care with the local public health TB Control Clinic for follow-up purposes and medication refills. However, the patient was reported by his work-related acquaintances to have moved back to Africa shortly after discharge without picking up any medications from the health department or following up in clinic. His course in Africa is unknown as he did not keep in touch with these acquaintances after moving back to Africa.

Discussion

Tuberculous meningitis is a rare but deadly disease in the United States. Risk factors are similar to those of pulmonary TB, including poverty, malnutrition, overcrowding, a compromised immune system, and coming from an endemic area [7]. It is very rare in immunocompetent patients.

Clinical presentation is highly variable, ranging from a rapidly progressive meningitis syndrome to slowly progressive dementia. However, some commonalities have been identified. According to one seminal review, a prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and personality changes can be seen and may persist for a few weeks, after which patients can then develop severe headaches, altered mental status, and cranial neuropathies. Seizures are uncommon manifestations of tuberculous meningitis in adults. Classic features of bacterial meningitis, such as stiff neck and high-grade fever, may be absent [8].

Cerebrospinal fluid examination is the mainstay of diagnosis of tuberculous meningitis. The examination of cerebrospinal fluid specimens is of critical importance to early diagnosis of tuberculous meningitis. CSF typically shows elevated protein and lowered glucose concentrations with a lymphocytic pleocytosis [9]. However, polymorphonuclear leukocyte predominance may be seen early in the disease, as was seen in our patient. Acid fast smear and culture are an essential component of diagnosis of tuberculous meningitis. CSF specimens should also be submitted for *Mycobacterium tuberculosis* complex nucleic acid testing with polymerase chain reaction technique, as this has been shown to be a very reliable test. In one report, it was found to have 81% sensitivity and 98% specificity [10].

Radiography, including CT and magnetic resonance imaging of the head, can sometimes be helpful in diagnosis. However, CT is neither sensitive nor specific [11]. Though magnetic resonance imaging is considered to be better than CT for the detection of tuberculous meningitis, it may not detect any abnormalities early on in the disease. Moreover, the characteristic imaging findings in tuberculous meningitis, including leptomeningeal and basal cisternal enhancement, ventriculomegaly due to hydrocephalus, periventricular infarcts, and the presence of tuberculomas, are not specific. They can be found in other diseases, including partially treated pyogenic meningitis, cryptococcal meningitis, and viral encephalitis, to name a few [12].

Treatment begins with a four-drug regimen including isoniazid, rifampin, pyrazinamide, and either a fluoroquinolone or an injectable aminoglycoside. This four-drug regimen is continued for two months, followed by isoniazid and rifampin alone lasting about 9 to 12 months. However, given the lack of sufficient data on optimal duration, the treatment should be tailored to each individual case depending on clinical response, drug sensitivity, and other individual patient circumstances [13]. Ethambutol is not typically used for tuberculous meningitis, as it has poor penetration into the meninges, even when the meninges are inflamed [14]. Based on expert opinion, the official American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Disease Society of America guidelines, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy [13].

A randomized controlled trial and subsequently a Cochrane review including seven clinical trials and 1,140 participants showed that adjunctive glucocorticoid therapy helps reduce mortality in HIV-uninfected patients at an early stage of the disease. The benefit in mortality rates only approached significance for mid to late disease. No mortality benefit from glucocorticoid therapy was evident in HIV-infected patients included in the study [15,16]. In retrospect, our patient may have qualified for adjunctive steroids since he was negative for HIV and was likely early on in the disease as evidenced by the relative neutrophil predominance in his CSF cell count differential. However, the trials that showed clinical benefit administered glucocorticoid therapy for at least 6–8 weeks. Our patient received less than a week of anti-tuberculous therapy, and did not follow-up with treatment upon discharge. Thus, it is unclear if our patient would have benefited significantly from glucocorticoid therapy given that he would have received less than a fraction of the recommended duration prior to being lost to follow-up.

This case is a rare situation where tuberculous meningitis was diagnosed in an immunocompetent host in the United States. Though there have been a few case reports and articles discussing tuberculous meningitis in the immunocompetent host in developing nations where the disease is endemic [17–20], it is very rare to find such reports in the United States. [21]. The same can be said about other forms of extrapulmonary TB. Though there are reports of breast TB [22], colonic TB [23], skeletal TB [24], and other forms of extrapulmonary TB in endemic countries, finding such reports in non-endemic countries is very rare. This suggests that contracting extrapulmonary TB increases in frequency in immunocompetent hosts that have been exposed to endemic areas (either immigrating from or traveling to these areas), but is still rare as compared to extrapulmonary TB in immunocompromised individuals. Pulmonary TB, on the other hand, is found commonly in both immunocompetent and immunocompromised individuals.

This case questions the conventional view that tuberculous meningitis happens in only immunocompromised individuals. Further research should be done to investigate in more detail this subset population (immunocompetent individuals) that develop tuberculous meningitis and in fact other forms of extrapulmonary TB to better understand the pathophysiology of these diseases in the immunocompetent host, as currently such knowledge is lacking

Conclusions

Given the rarity of tuberculous meningitis in immunocompetent patients in the United States this case emphasizes the importance of maintaining a strong clinical suspicion of the diagnosis in patients with risk factors and an indolent course of disease presentation even if they are immunocompetent and live in geographic areas with low disease prevalence. The importance of early diagnosis and treatment of patients with tuberculous meningitis in improving outcomes is well known. Untreated tuberculous meningitis is associated with a high frequency of neurologic sequelae and mortality if not treated promptly [25].

References:

1. Henry M, Hlzman RS: Tuberculosis of the brain, meninges, and spinal cord. In: Rom WN, Garay SM et al. (eds.), Tuberculosis. 2nd edition. Philadelphia, Pa, USA: Lippincott Williams & Wilkins, 2004; 445–64
2. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2014. US Department of Health and Human Services, Atlanta, GA 20104
3. TB Country Profile, Senegal. World Health Organization. *https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=SN&LAN=EN&outtype=pdf. Last updated 3/22/16*
4. Reported Estimates of BCG Coverage. World Health Organization. *http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragebcg.html. Last updated 7/15/16*
5. Marx GE, Chan ED: Tuberculous meningitis: Diagnosis and treatment overview. Tuberc Res Treat, 2011; 2011: 798764
6. Kent SJ, Crowe SM, Yung A et al: Tuberculous meningitis: A 30-year review. Clin Infect Dis, 1993; 17(6): 987–94
7. Lawn SD, Zumla AI: Tuberculosis. Lancet, 2011; 378: 57–72
8. Udani PM, Dastur DK: Tuberculous encephalopathy with and without meningitis. Clinical features and pathological correlations. J Neurol Sci, 1979; 10(6): 541–61
9. Karandanis D, Shulman JA: Recent survey of infectious meningitis in adults: Review of laboratory findings in bacterial, tuberculous, and aseptic meningitis. South Med J, 1976; 69(4): 449–57
10. Denkinger CM, Schumacher SG, Boehme CC et al: Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: A systematic review and meta-analysis. Eur Respir J, 2014; 44(2): 435–46
11. Ozates M, Kemaloglu S, Gurkan F et al: CT of the brain in tuberculous meningitis, a review of 289 patients. Acta Radiol, 2000; 41(1): 13–17
12. Garg RK, Malhotra HS, Jain A: Neuroimaging in tuberculous meningitis. Neurol India, 2016; 64(2): 219–27
13. Blumberg HM, Burman WJ, Chaisson RE et al. American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society of America: Treatment of tubercuolosis. Am J Respir Crit Care Med,2003; 167(4): 603–63
14. Donald PR: Cerebrospinal fluid concentration of antituberculosis agents in adults and children. Tuberculosis (Edinb), 2010; 90(5): 279–92
15. Thwaites GE, Nguyen DB, Nguyen HD et al: Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med, 2004; 351(17): 1741–51
16. Prasad K, Singh MB: Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev, 2008; (1): CD002244
17. Akyol AG, Nazliel B, Oner Y, Erdem O: Chronic bilateral hearing loss in an immunocompetent patient. An atypical course of tuberculous meningitis. Neurosciences (Riyadh), 2014; 19(4): 322–25
18. Verma R, Patil TB, Lalla R: Disseminated tuberculosis manifesting as pulmonary, meningeal, and spinal tuberculosis in an immunocompetent patient. BMJ Case Rep, 2012; 2012: pii: bcr2012007778
19. Cagatay AA, Caliskan Y, Aksoz S et al: Extrapulmonary tuberculosis in immunocompetent adults. Scand J Infect Dis, 2004; 36(11–12): 799–806
20. Louvel D, Babo P, Sollet JP et al: Tuberculous meningitis in an immunocompetent adult: Contribution of cerebral imaging techniques to the diagnosis and follow-up. Rev Neurol (Paris), 1999; 155(11): 945–53
21. Hilal T, Hurley P, McCormick M: Disseminated tuberculosis with tuberculous meningitis in an immunocompetent host. Oxf Med Case Reports, 2014; 2014: 125–28
22. Kumar M, Chand G, Lakshmi Nag V et al: Breast tuberculosis in immunocompetent patients at tertiary care center: A case series. J Res Med Sci, 2012; 17(2): 199–202
23. Zubieta-O'Farrill G, Castillo-Calcaneo Jde D, Gonzales-Sanchez C et al: Colonic tuberculosis in an immunocompetent patient. Int J Surg Case Rep, 2013; 4(4): 359–61
24. de Araujo PS, de Melo HR, de Melo FL et al: Multifocal skeletal tuberculosis in an immunocompetent patient: A case report. BMC Infect Dis, 2015; 15: 235
25. Bidstrup C, Andersen PH, Skinhøj P, Andersen ÅB: Tuberculous meningitis in a country with a low incidence of tuberculosis: Still a serious disease and a diagnostic challenge. Scand J Infect Dis, 2002; 34(11): 811–14