Case Report

Mycobacterium tuberculosis and Cryptococcus neoformans co-infection meningitis in a young immuncompetent woman

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Abstract

Objectives: Meningitis is a severe and potentially fatal form of tuberculosis. The diagnostic workup involves detection of acid-fast bacilli (AFB) in the cerebrospinal fluid (CSF) by microscopy or culture. However, the difficulty in detecting the organism poses a challenge in diagnosis. Cryptococcosis is an opportunistic fungal infection caused by cryptococcus neoformans. We presented central nervous system co-infection of tuberculosis and Cryptococcus neoformans which is extremely rare.

Patient: The patient was a 35 year-old woman who was admitted in hospital due to fever, headache and changes of mental status. Physical examination revealed neck stiffness and positive Kernig's and Brudsinsky's signs. Cerebrospinal fluid analysis showed lymphocytic pleocytosis and culture of cerebrospinal fluid revealed mycobacterium tuberculosis and cryptococcus neoformans.

Conclusion: Tuberculosis meningitis should be considered in patients with chronic meningitis especially in endemic areas. Cryptococcus neoformans meningitis may occur in immunocompromised and immuncompetent patients. Central nervous system co-infection with tuberculosis and Cryptococcus neoformans is possible.

Keywords: Chronic Meningitis, Cryptococcus neoformans, Mycobacterium tuberculosis

Introduction

Mycobacterium tuberculosis is one of the most infectious agents in the world. It causes an insidious form of meningitis characterized by headache, low grade fever, stiff neck, cranial nerve palsies, and focal neurologic deficits (1). Careful evaluation of symptoms and CSF finding is the only way to establish an early diagnosis and reduce sequelae (2). Apart from that, cryptococcal infection of the brain is commonly seen in immunocompromised patients but rarely considered as the differential diagnosis in immunocompetent patients (3). We presented an extremely rare case with central nervous system co-infection with tuberculosis and Cryptococcus neoformans.

Case presentation

The patient was a 35 year-old housewife woman who was admitted to hospital due to fever, headache and changes of mental status. She had history of headache since several weeks ago. On admission her vital signs were as followed: T=37°C, PR=80/min, RR=15/min, BP=110/70 mmHg. In physical examination, she had neck stiffness as well as positive Kernig's and Brudsinsky's signs. Physical examination of chest, heart, abdomen and extremities were normal. She was drowsy and disoriented to time, place and person. Cranial nerves examination and deep tendon reflexes were normal. Plantar reflexes were downward. Brain CT scan without contrast was normal. Lumbar puncture was performed and cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis; WBC =188, lymphocyte: 90%, PMN: 10%, glucose= 41 mg/dl, concomitant blood sugar= 105 mg/dl, protein= 80 mg/dl. CSF smear showed no microorganisms and CSF culture was negative after 48 hours.

Laboratory data were as follows:

CBC: WBC=6300, Hb=12.2 g/dl, Plt=152,000, BUN=18 mg/dl, Cr=0.7 mg/dl, Na=136 meq/L, K=4.5 meq/L, FBS=72 mg/dl. ALT=19 U/L, AST=13 U/L, amylase= 45 U/L, PT=12.5s, PTT= 28s, INR=1. ESR= 63 mm, RF: negative, PPD test= 10 mm positive.

Chest-x-ray, paranasal sinuses x-ray and abdominopelvic sonography were not remarkable. Smear of CSF for Mycobacterium tuberculosis was negative but due to CSF analysis pattern (moderate WBC count, lymphocytic pleocytosis and low glucose level and high protein level) and according to endemicity of tuberculosis in this area, with the impression of tuberculosis meningitis, treatment with isoniazid, rifampin, ethambutol, pyrazinamide and Vitamin B6 was started. Additionally, corticosteroid was added to her treatment. In the first week of treatment, general condition improved minimally. We decided to repeat lumbar puncture to find out any change in pattern of CSF analysis and make decision to evaluate other causes of chronic meningitis. One week afterwards, lumbar puncture was performed again and CSF analysis with Indian ink staining was performed which was positive for Cryptococcus neoformans and confirmed later by culture on usual fungal media. Therefore, amphotericin B plus_flucytosinen were added to her treatment. Brain CT scan with contrast was performed that showed

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dilatation of lateral ventricles. After several weeks, CSF culture on Levenstein-johnson media was reported to be positive for Mycobacterium tuberculosis.

Further work-ups were performed to detect any evidence for immunodeficiency. Liver function test was within normal limits and HIV antibody, autoimmune and rheumatologic tests were negative. Bone marrow aspiration and biopsy were normal. The patient's level of conciseness gradually improved and after 15 weeks lumbar puncture was performed again that was normal: WBC= 0-1, RBC: 0-1, Glucose= 48mg/dl, concomitant blood sugar= 90 mg/dl Protein= 50mg/dl. Fluconazole was added to anti-tuberculosis drugs and she was discharged from hospital with good general condition and normal mental status. She had moderate bilateral sensoryneural hearing loss as a complication of meningitis.

Discussion

Tuberculous (TB) meningitis is a severe form of extra pulmonary tuberculosis of which exact incidence and prevalence are unknown. In countries with high burden of pulmonary tuberculosis, the incidence is expected to be proportionately high. Children are much more vulnerable and HIV-positive patients have a high incidence of TB meningitis (4). Moreover, cryptococcal infections occur frequently in immunocompromised patients particularly in the context of AIDS, lymphomas and following immunosuppression for organ transplant recipients. In these contexts, the infection is readily considered and diagnosis is straightforward. The diagnosis is rarer and thus less likely to be considered in immunocompetent patients which can lead to late diagnosis and delay in initiation of therapy (5). Cryptococcal meningitis and tuberculosis are leading causes of mortality in patients initiating antiretroviral therapy in Africa. It is hypothesized that a history of tuberculosis may predispose to the development of cryptococcal meningitis in Jarvis's study. History of pulmonary tuberculosis was independently associated with the development of cryptococcal meningitis after adjustment for covariates (6).

The hallmark pathological processes of TB meningitis are meningeal inflammation, basal exudates, vasculitis and hydrocephalus. Headache, vomiting, meningeal signs, focal neurologic deficits, vision loss, cranial nerve palsies and raised intracranial pressure are dominant clinical features (4). The top 7 manifestations of TB meningitis are: coma, onset of disease more than 5 days, lymphocyte predominant in CSF, glucose level in CSF 50% lower than that of blood, abnormal CT finding, abnormal ocular fundi and proved tuberculosis of another site (7). However, cryptococcal meningitis should be considered in cases of unexplained headache, altered vision, altered mental status, nausea and fever (8). The lack of specific symptoms and signs in patients with TB meningitis makes early diagnosis difficult (6). Diagnosis is based on the characteristic clinical picture, neuroimaging abnormalities and CSF changes (increased protein, low glucose and mononuclear cell pleocytosis). CSF smear examination, mycobacterial culture or polymerase chain reaction (PCR) is mandatory for bacteriological confirmation (4). Definitive diagnosis of TB meningitis depends upon the detection of the tubercle bacilli in the CSF (9).

According to high mortality and morbidity of TB meningitis, prompt diagnosis and early treatment are crucial (4). CSF adenosine deaminase activity (ADA) can be used for diagnosis of TB meningitis while CSF ADA> 8.0 U/L has sensitivity and specificity of 80% and 90%, respectively (6). In addition, diagnosis of Cryptococcus meningitis is established by isolation of cryptococcus neoformans in culture, staining with India ink and evidence of latex antigen agglutination in CSF (10). Decision to start anti-TB treatment is often empirical and guidelines recommended a prolonged treatment extended to 9 or 12 months to avoid anti-TB drug resistance that is associated with high fatality. Besides, corticosteroids reduce the mortality rate and patients with hydrocephalus may need ventriculo-peritoneal shunting (4).

Cryptococcal meningitis is one of the most common life-threatening fungal infections and is associated with high mortality. Amphotericin B plus flucytosine and fluconazole is the current optimal therapy (11).

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