A Patient Presenting with Tuberculous Encephalopathy and Human Immunodeficiency Virus Infection

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Data Collection B
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Patient:	**Male, 33**
Final Diagnosis:	**Tuberculous meningitis, human immunodeficiency virus infection**
Symptoms:	**—**
Medication:	**—**
Clinical Procedure:	**Lumbar puncture**
Specialty:	**Infectious Diseases**

Objective:	**Rare disease**
Background:	In the USA, *Mycobacterium tuberculosis* infection is more likely to be found in foreign-born individuals, and those co-infected with human immunodeficiency virus (HIV) are more likely to have tuberculous meningitis. The literature is lacking in details about the clinical workup of patients presenting with tuberculous meningitis with encephalopathic features who are co-infected with HIV. This report demonstrates a clinical approach to diagnosis and management of tuberculous meningitis.
Case Report:	A 33-year-old Ecuadorean man presented with altered consciousness and constitutional symptoms. During the workup he was found to have tuberculous meningitis with encephalopathic features and concurrent HIV infection. Early evidence for tuberculosis meningitis included lymphocytic pleocytosis and a positive interferon gamma release assay. A confirmatory diagnosis of systemic infection was made based on lymph node biopsy. Imaging studies of the neck showed scrofula and adenopathy, and brain imaging showed infarctions, exudates, and communicating hydrocephalus. Treatment was started for tuberculous meningitis, while antiretroviral therapy for HIV was started 5 days later in combination with prednisone, given the risk of immune reconstitution inflammatory syndrome (IRIS).
Conclusions:	A clinical picture consistent with tuberculous meningitis includes constitutional symptoms, foreign birth, lymphocytic pleocytosis, specific radiographic findings, and immunodeficiency. Workup for tuberculous meningitis should include MRI, HIV screening, and cerebral spinal fluid analysis. It is essential to treat co-infection with HIV and to assess for IRIS.
MeSH Keywords:	**HIV Infections • Immune Reconstitution Inflammatory Syndrome • Tuberculosis, Meningeal**
Full-text PDF:	**http://www.amjcaserep.com/abstract/index/idArt/897745**

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Background

According to the World Health Organization, approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* (TB) [1], making it a huge global health burden. Tuberculous meningitis, a form of extrapulmonary TB (21% of total), is the most lethal, accounting for 5.2% of all extrapulmonary cases [1]. According to the Centers for Disease Control and Prevention, the number of TB cases reported annually has been decreasing in the USA, but the rates of tuberculosis in foreign-born individuals remains high [2], especially among those with concomitant risk factors such as HIV infection [3]. Particularly, TB rates for African Americans, Hispanics, American Indians, Pacific Islanders, and whites were 5.1, 5, 5, 16.9, and 0.6 cases per 100 000 persons, respectively [2]. Of 43 519 people with acquired immunodeficiency syndrome (AIDS) born in the USA, 1013 (2.3%) were also diagnosed with extrapulmonary TB [3]. In comparison, 82 (13%) of 648 people with AIDS born in Haiti, 26 (8%) of 343 born in Mexico, and 4 (1%) of 412 born in Cuba had extrapulmonary TB [3]. Hispanic ethnicity, compared to white males, was associated with an odds ratio of 1.6 for developing both extrapulmonary TB and AIDS [3]. Encephalopathic findings (e.g., altered mentation, convulsions, involuntary movements, and paralysis), which are indicative of frank infarction secondary to involvement of large basal arteries, are relatively more common in developing countries [4]. In patients with HIV and TB meningitis, encephalopathic features are more common [5]. The literature is lacking in details about the clinical workup of patients presenting with tuberculous meningitis with encephalopathic features who are co-infected with the HIV. This report uniquely demonstrates a clinical approach to diagnosis and management of tuberculous meningitis with encephalopathic features and interesting radiologic findings.

Case Report

A 33-year-old Ecuadorean man presented to the Emergency Department with obtundation, diaphoresis, and aphasia for the past 4 hours. A history was obtained from his sister, who stated that the patient had been experiencing symptoms of headache, weakness, myalgias, and weight loss over the past 3 weeks. He had emigrated from Ecuador to New York state about 8 years ago and worked in carpentry. His past medical history, social history, and family history were unremarkable.

Vital signs were the following: temperature 32.2°C (rectal), pulse rate 43 per min, blood pressure 80/60 mmHg, respiratory rate 16 per min, and oxygen saturation 96% on 2-L nasal cannula. His hypotension responded to normal saline fluid hydration. Physical examination of the heart, lungs, abdomen, pupils, deep tendon reflexes, and muscle tone were within normal limits. Except for a sodium level of 132 mmol/L (averaging 125 mmol/L over the
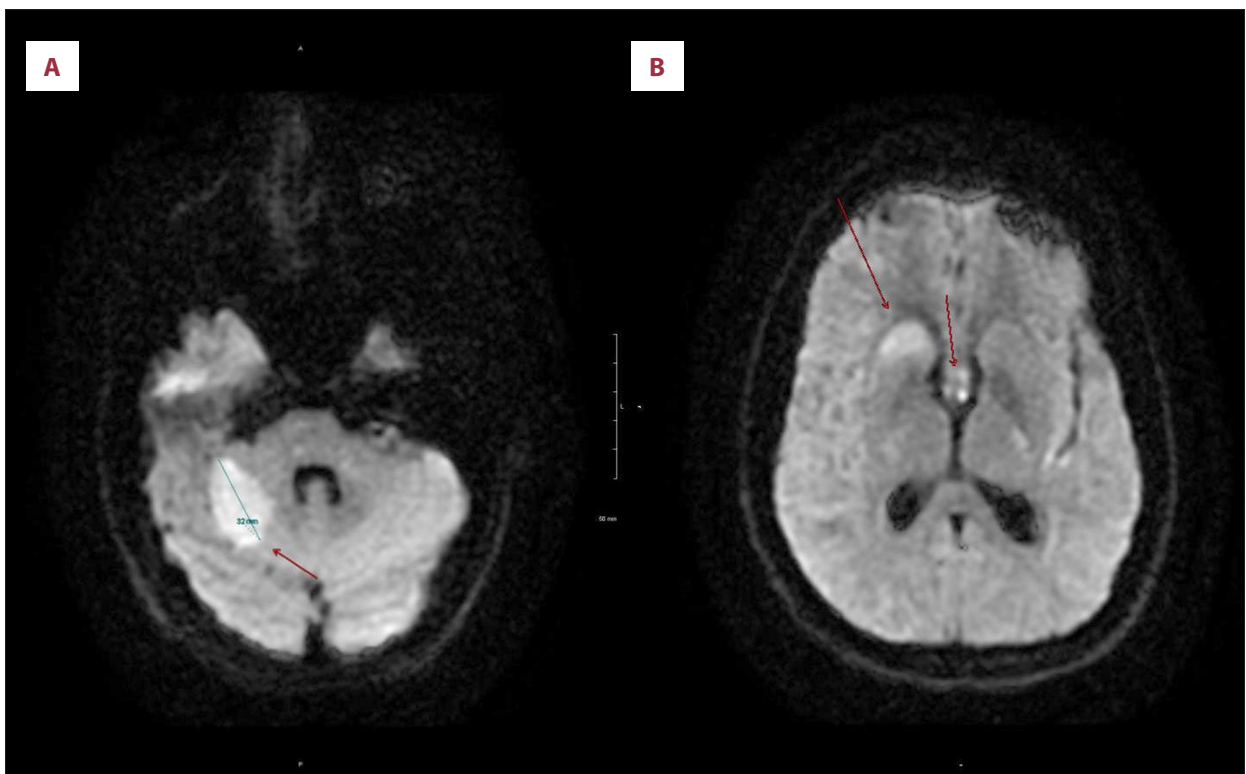

Figure 1. MRI diffusion-weighted axial image demonstrating (**A**) right cerebella infarct; (**B**) exudates at the floor of the brain.
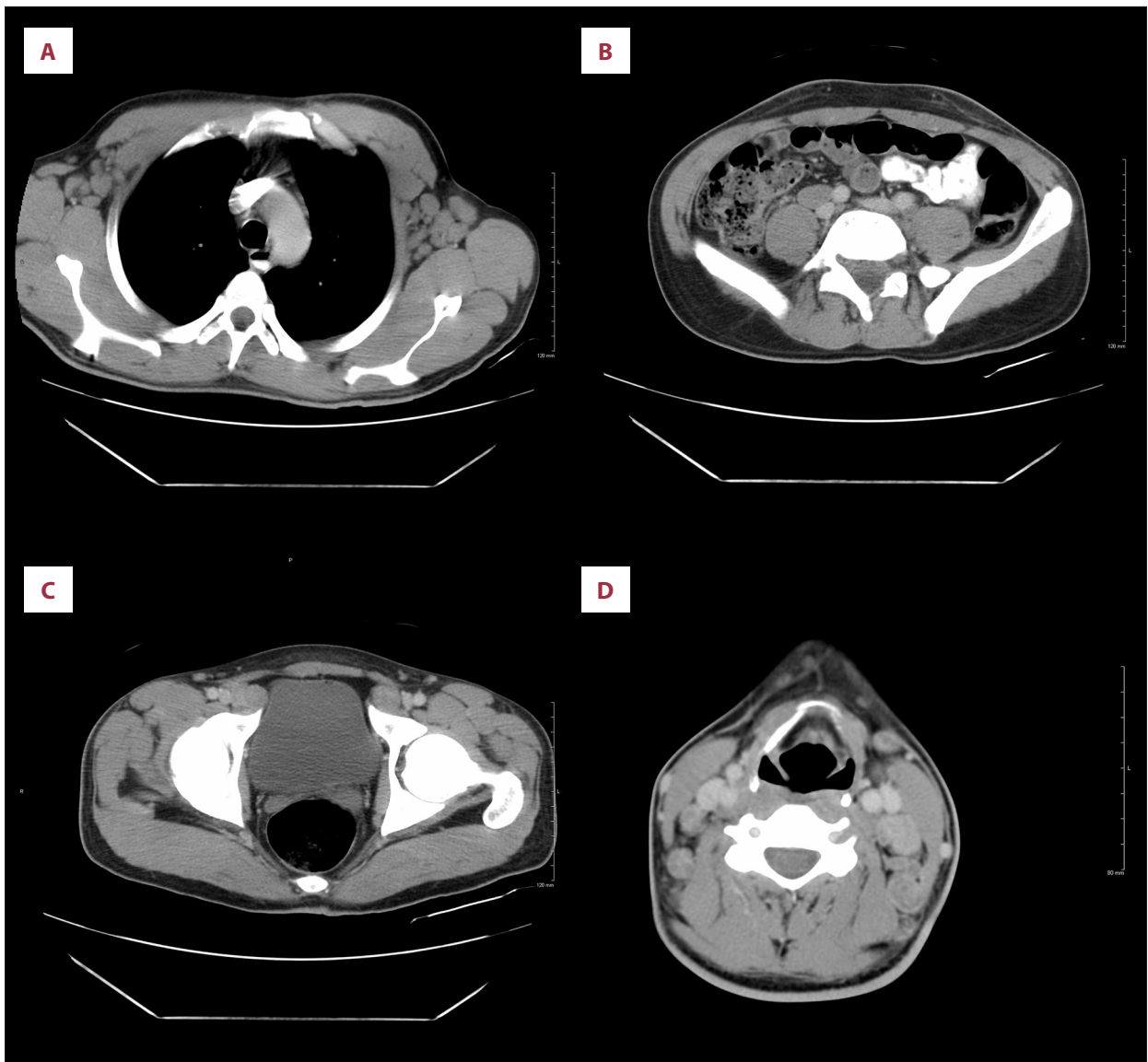
Figure 2. Non-contrast CT axial image demonstrating (**A**) axillary lymphadenopathy; (**B**) enlargement of the lymph nodes adjacent the right common iliac artery; (**C**) inguinal lymphadenopathy; (**D**) cervical lymphadenopathy with necrotic features.

course of his stay), his complete blood count, electrolyte levels, urinalysis, urine toxicology, electrocardiogram, and chest radiograph showed no abnormalities. Computed tomography (CT) of the brain without contrast showed no evidence of acute large-vessel occlusive infarction or hemorrhage. Cerebrospinal fluid (CSF) analysis showed white blood cell count of 91 with 97% lymphocytes, protein level of 158 mg/dL, and glucose level of 20 mg/dL, with a negative acid-fast stain.

Further workup for encephalopathy included magnetic resonance imaging (MRI) of the brain without contrast. Acute infarctions were found, with involvement of the right caudate nucleus, anterior commissure, right superior cerebellar peduncle, and right cerebellar hemisphere with no evidence of hemorrhage

(Figure 1). With high suspicion for TB, interferon gamma release assay (QuantiFERON®TB Gold; Qiagen) was performed and the result was positive. The patient was started on a 4-drug regimen for TB, which includes rifampin (10 mg/kg daily), pyrazinamide (23 mg/kg daily), ethambutol (18 mg/kg daily), and isoniazid (5 mg/kg daily). CT scans of the neck, chest, abdomen, and pelvis showed enlarged lymph nodes in the axillary, common iliac, inguinal, and cervical regions (Figure 2A–2D). Confirmation for systemic TB infection was sought: a sub-centimeter right axillary lymph node was biopsied, with findings of caseous necrosis, acid-fast staining bacilli, and positive *Mycobacterium tuberculosis* culture. TB cultures were sensitive to the 4-drug regimen for TB. Testing for HIV was performed: CD4 count was 274 cells/mm^3 and HIV antibody was reactive at >50 with a viral
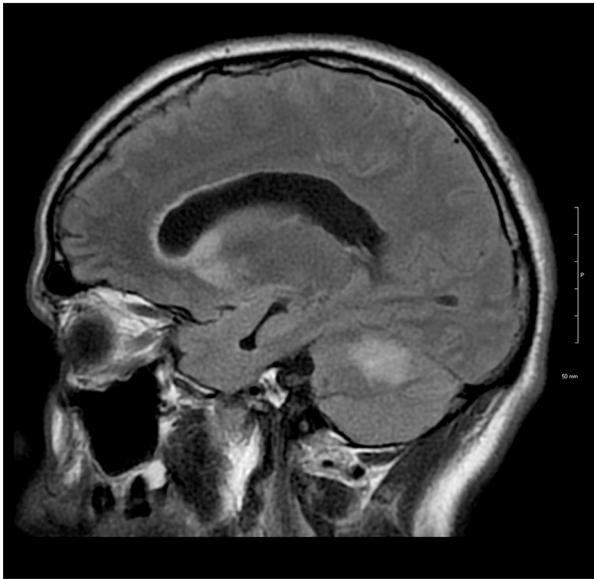
Figure 3. MRI flair sagittal image demonstrating infarction of the basal ganglia, floor of the frontal lobe above the hypothalamus, right superior cerebellum, and cerebellar vermis.

load of 303 390 by RNA PCR. Sulfamethoxazole-trimethoprim (800–160 mg; twice daily) was started for *Pneumocystis* prophylaxis, given the high viral load. Highly active antiretroviral therapy (Emtricitabine 200 mg daily, Tenofovir 300 mg daily, and Raltegravir 400 mg twice daily) was started 5 days after the start of TB treatment. Prednisone (1 mg/kg daily) was added to the regimen to prevent IRIS. Further workup showed

hypo-osmolar euvolemic hyponatremia, consistent with the syndrome of inappropriate antidiuretic hormone. Adrenal insufficiency was less likely given that he was normotensive on admission. He was restricted to less than 1 liter of fluid intake per day and given and sodium chloride tablets to correct for hyponatremia. Tests were negative for syphilis, St. Louis encephalitis virus, West Nile virus, herpes simplex virus, Lyme disease, and Coxsackie A7, 9, 16, and 24, and B1–6.

One month after admission, the patient's mental status showed moderate improvement. He was responsive to verbal commands but nuchal rigidity and confusion persisted. MRI of the brain without IV contrast at this time showed infarction in the basal ganglia, floor of the frontal lobes above the hypothalamus, and superior cerebellar vermis, (Figure 3). In addition, signs of communicating hydrocephalus on MRI were found (Figure 4). Following a family meeting, the patient was discharged home under the care of his family. Six months following discharge, he showed improved mental status.

Discussion

Early evidence for TB infection included lymphocytic pleocytosis and a positive interferon gamma release assay. A confirmatory diagnosis of TB was made based on positive culture, caseous necrosis, and acid-fast bacilli in the right axillary lymph node biopsy specimen. The imaging studies of the neck showed hypodense centers most consistent with scrofula and adenopathy (Figure 2D), while brain imaging showed infarctions (Figure 3),
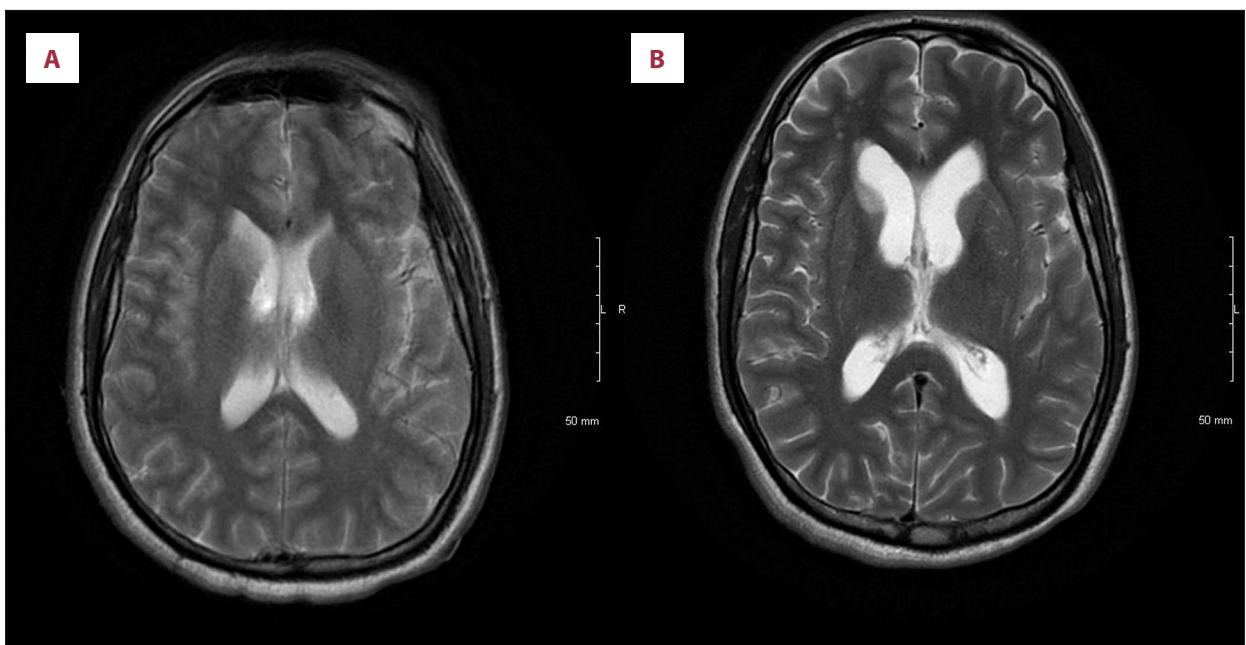

Figure 4. (**A, B**) MRI T2-weighted axial image showing rapid development of a communicating hydrocephalus over the course of 25 days.

exudates at the floor of the brain (Figure 1B), and communicating hydrocephalus (Figure 4). These findings, combined with symptoms of headache, weight loss, and decreased consciousness, confirmed the diagnosis of TB meningitis with encephalitic features. Hyponatremia was thought to be due to syndrome of inappropriate antidiuretic hormone, which is seen in 45% of TB meningitis patients, and is generally associated with a poor clinical outcome.

Tuberculosis of the CNS, while uncommon [6], is classified on the basis of the following findings: cerebral abscess, tuberculomas [7,8], meningitis [7,10,11], and myelopathy [12–14]. Tuberculous meningitis, an important neurologic complication associated with HIV infection, has been well described in Africa [15] but reports are lacking in the USA.

CNS infarctions and communicating hydrocephalus are common findings in TB meningitis and are well described in the medical literature [16,17]. Hydrocephalus and infarctions are seen on CT scans in 12% and 28%, respectively, of adults with TB meningitis [18,19]. These infarctions are likely linked to compression and inflammation of large basal arteries secondary to histiocytic proliferation and adhesive meningitis found on tissue analysis [16]. Udani and Dastur (1970) [4] described tuberculous encephalopathy with and without meningitis presenting with diffuse features of brain involvement, including changes in level of consciousness, convulsions, involuntary movements, paralysis, and pyramidal/extrapyramidal and cerebellar signs. Pathology evidence were found for miliary, intracranial, intrathoracic and abdominal tuberculosis in 23%, 50%, 37%, and 27%, respectively [4]. While well described in the literature [16], tuberculous meningitis with encephalitic features is an uncommon presentation in patients in the USA.

Making a diagnosis of TB meningitis based solely on laboratory criteria can be difficult because co-infection with HIV makes the diagnosis challenging. Multiple studies have demonstrated increased incidence of TB meningitis in HIV-infected patients [9,20–22] because HIV infection is a strong risk factor for the progression of TB from asymptomatic to systemic infection [23], a risk which increases as CD4 counts decline [7]. Co-infection with HIV also modifies the lab findings because patients may present with acellular CSF and higher AFB loads [21]. However, Berenguer et al. [10] and Dube et al. [11] showed that TB meningitis clinical manifestations, CSF findings, and response to therapy were similar for those with and without HIV infection. A study of 53 adults suggested that HIV infection did not alter the clinical features of TB meningitis, although the cognitive dysfunction was more severe in patients co-infected with HIV [22]. The study found that HIV-infected patients did not develop tuberculoma and demonstrated less basal meningeal enhancement and hydrocephalus as compared with HIV-negative patients [22]. HIV infection is associated with higher rates of infarction and lower rates of hydrocephalus in patients with TB meningitis [5,24]. Interestingly, while our patient did not have tuberculomas, he had basal meningeal enhancement, infarctions, and hydrocephalus.

Paradoxical TB-immune reconstitution inflammatory syndrome (IRIS) has been described in the literature as an inflammatory response in the context of the recovering immune system in HIV patients. The clinical features of this condition include new or worsening meningitis, tuberculomas, and tuberculous brain accesses. Previous case reports and case series have shown the usefulness of prednisone for treatment of TB-IRIS [25]. The benefit of corticosteroid treatment for TB meningitis in HIV-infected patients is inconclusive, based on a recent review [26]. In the first prospective study of patients with HIV infection and TB meningitis [27], starting prednisone prior to HIV treatment did not significantly decrease the occurrence of TB-IRIS. Because of the relatively small sample size (34 patients), the present study may not have had sufficient statistical power to detect the effect of prednisone on the occurrence of IRIS [27]. While not shown to prevent TB-IRIS, prednisone was added to the regimen given the significant risk for TB-IRIS. The timing for starting highly active antiretroviral therapy should be balanced with the risk of developing opportunistic infections. In our patient, the HIV medications were started 5 days after the TB medications. This is considered early antiretroviral treatment (less than seven days after TB treatment) compared to delayed treatment (2 months after TB treatment) [25].

Conclusions

In patients presenting with constitutional symptoms and encephalopathic features, a high index of suspicion should be maintained for tuberculous meningitis and workup should include MRI screening, testing for HIV infection, and cerebral spinal fluid analysis. Regions in which TB is common, including the Caribbean, Pacific Islands, and South American countries, may also have higher prevalence of HIV infection, making the country of birth a significant part of the medical history. Treatment should be started based on a clinical picture consistent with tuberculous meningitis, which includes constitutional symptoms, foreign birth, lymphocytic pleocytosis, specific radiographic findings, and immunodeficiency. It is essential to treat co-infection with HIV and to address the possibility of immune reconstitution inflammatory syndrome. This case report should contribute toward the development of an organized approach to timely diagnosis and management of tuberculous meningitis.

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