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Case Report

Cryptococcal meningitis with suspected concomitant neurosyphilis in an immunocompetent individual: A diagnostic dilemma

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Introduction

Cryptococcal meningitis (CM) and neurosyphilis occur in regions with a high prevalence of human immunodeficiency virus (HIV) infection [1,2]. Occurrence in immunocompetent individuals is rare. Non-specific clinical features often lead to a delay in diagnosis. Hence, appropriate in-depth evaluation is of paramount importance. Herein we present a case of a 22-year-old immunocompetent male with CM and suspected concomitant neurosyphilis.

Case Report

A 22-year-old male from the Southern Province of Sri Lanka presented with a history of chronic headache for 2 months, bilateral lower limb weakness for 2 weeks and altered behaviour for 3 days' duration. Detailed description of symptoms could not be obtained as the patient had a reduced level of consciousness on admission. According to the collateral history, he had an intermittent, nonspecific headache without any associated fever, vomiting, limb weakness, convulsions, vertigo, syncope or impaired consciousness at the initial stage. He had self-medicated with simple analgesics, intermittently. He complained of progressive weakness of bilateral lower limbs 2 weeks prior to admission and became bed bound within the course of 2 weeks. He also complained of poor vision for the same duration. Medical treatment was not sought, and spiritual activities were carried out. He was admitted to the local hospital only when he developed altered level of consciousness for 3 days. He was brought against medical advice to our tertiary care hospital the following day. He had very

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poor family support, being the 8th of 10 siblings, and he had been brought up by a relative during childhood. According to his family, he had left home 4 months ago and lived with a friend who was known to be an illicit drug abuser. Although his family assured us that he never consumed alcohol, abused illicit drugs or had high risk sexual behaviour, they had a poor relationship with him.

On admission, his Glasgow coma scale (GCS) was E4/V4/M6 – 14/15. He was disoriented and confused. His blood pressure was 130/80 mmHg, heart rate 98 bpm, respiratory rate 20 breaths per minute, oxygen saturation 98% on room air. He had multiple tattoos. There was significant neck stiffness and a positive Kernig's sign. Bilateral pupils were dilated 6mm; reactive to light. Cranial nerves were difficult to assess, but bilateral lateral rectus palsy was noted. Diminished tone was noted in bilateral lower limbs with power 3/5, and diminished tendon reflexes. Tone in upper limbs was normal and power was 4/5 with preserved reflexes. Rest of the cardiovascular, abdominal, respiratory system examinations were unremarkable. There were no skin rashes, or genital ulcers.

Initial evaluation revealed a neutrophil leucocytosis with a white cell count of 15 x 10^3/uL, haemoglobin 13.3 g/dL and platelets of 323 x 10^3/uL. Erythrocyte sedimentation rate and C-reactive protein were 26 mm in 1 hour and <5 mg/L respectively. Blood picture, liver and renal profiles were unremarkable. Blood, urine, and sputum cultures were sterile. Non contrast computed tomography of brain was normal. Lumbar puncture revealed a high protein concentration of 236 mg/dL with a very low glucose level of 10 mg/dL. There were 70/cumm polymorphs, 5/cumm lymphocytes and 110/ cumm red cells.

A provisional diagnosis of bacterial meningitis was made, and he was started on intravenous ceftriaxone and intravenous dexamethasone. CSF for *N. meningitidis* and *H. influenzae* antigens was negative. CSF bacterial cultures were sterile. Considering his prolonged course of illness, and abnormal CSF analysis, fungal and tuberculous (TB) screening was carried out. CSF acid-fast bacilli (AFB) stain was negative; and so was the *Mycobacterium tuberculosis* polymerase chain reaction (PCR). However, India ink staining of the CSF sample revealed spherical yeast cells with a surrounding halo. Cryptococcal antigen was detected in the CSF. CSF culture in Sabouraud dextrose agar (SDA) revealed a growth of cream-coloured, mucoid colonies suggestive of *Cryptococcus*. (Figure 1) His magnetic resonance imaging (MRI) of brain revealed acute and subacute infarcts in bilateral caudate and lentiform nuclei, thalami, deep white matter adjacent to right frontal horn and bilateral corona radiate. Electroencephalogram depicted dominant theta slowing with intermittent delta slowing, compatible with mild degree encephalopathy.

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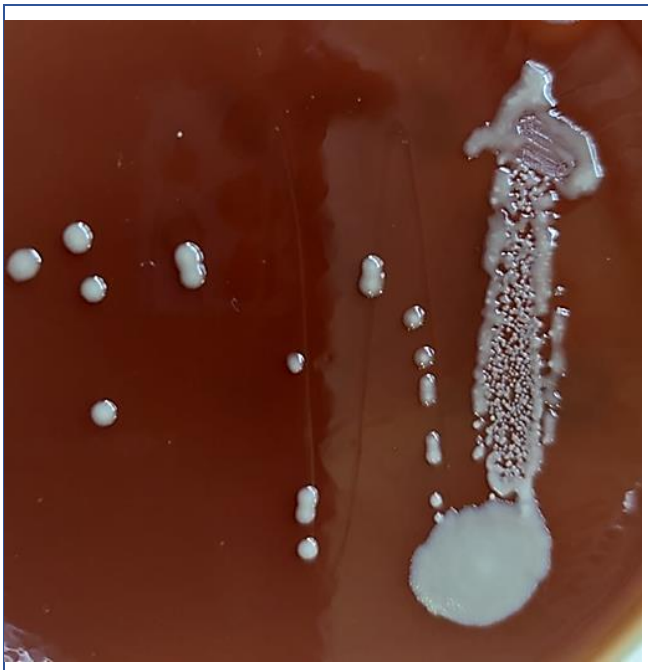

Figure 1: CSF culture in Sabouraud Dextrose Agar (SDA) revealed growth of cream-coloured mucoid colonies suggestive of *Cryptococcus* species

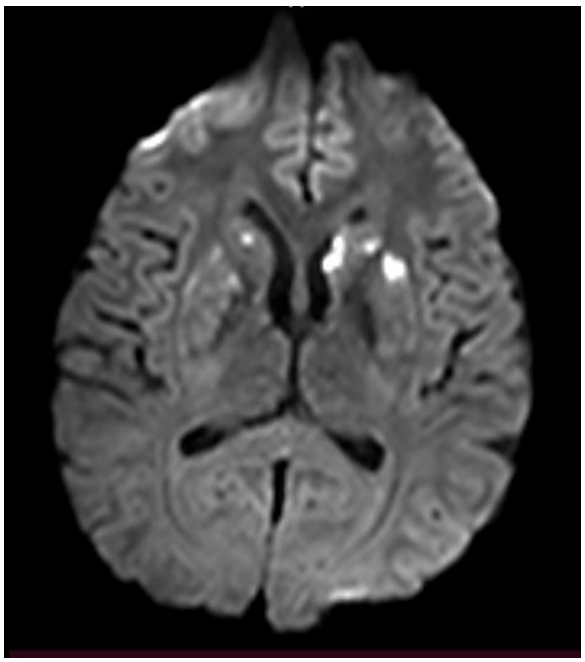

Figure 2: Diffusion weighted image of MRI brain showing infarcts in bilateral caudate nuclei and left lentiform nucleus

The patient was then screened for an underlying immunodeficiency state. HIV 1 & 2 antibodies checked using ELISA 4 were repeatedly negative. TB screening, including Mantoux and chest radiography, was negative. Melioidosis antibodies were not detected in either serum or CSF. He had no features of an underlying malignancy clinically or upon laboratory evaluation. Ultrasonography of abdomen and echocardiogram were unremarkable. He had no clinical features suggestive of an autoimmune disorder. His anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies were negative. Sexually transmitted infection screening revealed reactive serum VDRL (Venereal Disease Research Laboratory) and TPHA (*Treponema pallidum* Haemagglutination) assays. However, CSF VDRL was negative. Following multidisciplinary discussion, treatment with intravenous liposomal amphotericin B and intravenous benzyl penicillin was initiated. This was subsequently converted to oral fluconazole. Although he had some improvement in his cognition, his visual impairment and generalized weakness persisted. He was dependent on his activities of daily living even after 4 months of treatment.

Discussion

Cryptococcosis is an opportunistic fungal disease that causes infection commonly in immunocompromised, particularly in patients infected with HIV. Other risk categories include solid organ transplant recipients, patients with haematological malignancies, and

those on immunosuppressive therapy [3]. Clinical presentation of CM is variable. Onset of symptoms to presentation usually takes 6 to 12 weeks in non-HIV cases. Headache and altered mental status are typical symptoms. Meningism occurs in less than 20% of patients with CM [4]. Visual impairment, cranial nerve palsies and strokes are known complications. CSF analysis typically shows lymphocytic pleocytosis with high protein and low glucose levels (1). Diagnosis of CM can be made by the rapid cryptococcal antigen assay and CSF India ink staining test. CSF culture in SDA remains the gold standard which was positive in our patient confirming the diagnosis [3].

Neurosyphilis is a slowly progressive disease that can occur at any stage of syphilis. It can manifest as subacute meningitis due to meningeal involvement, stroke secondary to inflammatory vasculitis, tabes dorsalis and general paresis [5]. There are no gold standard criteria to diagnose neurosyphilis. CSF showing elevated polymorphs greater than 5 cells/mm^3 and protein levels greater than 40 mg/dL is consistent with the diagnosis [6]. A reactive CSF VDRL test is considered diagnostic of neurosyphilis but the diagnostic sensitivity is around 70% [6,7]. Thus, a negative CSF VDRL does not exclude neurosyphilis and it is better used to rule in rather than rule out neurosyphilis. Prior penicillin exposure may also have led to a false negative result.

As we were unable to confirm neurosyphilis in our patient, differentiating whether this was a case of CM with concomitant neurosyphilis or just a case of CM was a challenge. In the background of positive serology for syphilis, presence of suggestive clinical features, compatible CSF findings, radiological imaging suggestive of subacute infarcts which is a known presentation of neurosyphilis, and poor response to antifungals, led us to consider treating concomitant neurosyphilis giving the benefit of doubt to the patient. Although our patient was apparently immunocompetent, we had a strong suspicion of an underlying immunodeficiency state that we could not evaluate further due to financial constraints. Literature survey revealed cases of CM in apparently immunocompetent individuals who were subsequently found to have rare forms of immunosuppression such as anti-granulocyte-macrophage colony stimulating factor antibodies and idiopathic CD4 lymphocytopenia [8].

We managed our patient with IV liposomal amphotericin B for 14 days as induction therapy and fluconazole for 4 months as maintenance therapy. Simultaneously IV penicillin G was administered for 14 days followed by IM benzathine penicillin weekly for 3 weeks. Poor outcome in our patient may have been due to diffuse brain insult evidenced by sub-acute infarcts at the time of presentation, which was 2 months since onset of symptoms.

Conclusion

Our case highlights the importance of early presentation to medical care, early diagnosis and initiation of treatment. Clinicians need to have a broad differential diagnosis in patients with

nonspecific symptoms. This case also illustrates the importance of careful interpretation of laboratory tests in the relevant clinical context.

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