Disseminated Strongyloidiasis: Breaking Brain Barriers

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Abstract

Strongyloides stercoralis (SS) is one of the most overlooked helminthic infections despite being highly endemic in tropical and subtropical areas. In immunocompromised patients, especially those on long-term steroids, infection can often escalate to fatal dissemination into major organs. We present a compendium of two immunocompromised patients, who were on high-dose steroids and presented with worsening neurological status. Cerebrospinal fluid analysis was notable for larvae of SS as diagnosed by direct visualization. A syndrome of SS hyperinfection with dissemination was made after stool, and sputum samples also revealed SS larvae. SS is an elusive disease and should be considered early on, especially in endemic regions like India. Early diagnosis and prompt initiation of antihelminthic therapy is indispensable for favorable outcomes.

Keywords: Dissemination, hyperinfection, immunocompromised, meningitis, *Strongyloides stercoralis*

Introduction

Strongyloides infection was first reported as early as 1876 in French soldiers returning from duty in Indochina.[1] Strongyloidiasis is a ubiquitous infection, especially in tropical countries like India. The disease has a varied presentation from being asymptomatic to a fatal-disseminated disease involving multiple organs. Patients with suppressed cellular immunity such as those on chronic corticosteroid therapy or other immunosuppressants are at risk for the development of *Strongyloides stercoralis* (SS) hyperinfection and dissemination.[2] Brain and meningeal involvement with SS has been described in very few cases in literature and mostly postmortem.[3,4] To the best of our knowledge, no cases of cerebral strongyloidiasis have been reported from India. We report two cases of SS dissemination into the cerebrospinal fluid (CSF), diagnosed by direct visualization of the parasite in the CSF, both of whom completely recovered with timely treatment.

Case Reports

Case 1

MD is an 85-year-old female who presented with *de novo* status epilepticus. Her history was unremarkable except for Breast Carcinoma (CA) 5 years back treated with lumpectomy followed by external beam radiotherapy. On presentation, she was stuporous with minimal verbal and motor response to pain. Involuntary, jerky movements of the left upper limb with twitching of the left angle of mouth were noted. No other focal neurological deficits were present; reflexes were present, plantar responses were bilaterally extensor, and no meningeal signs were present.

Investigations

Metabolic causes were ruled out on routine blood investigations. Magnetic resonance imaging (MRI) brain revealed right temporoparietal and right thalamic/pulvinar hyperintensities [Figure 1a] and electroencephalography (EEG) showed right temporal spikes with burst suppression pattern [Figure 1b]. CSF analysis was essentially normal (white blood cells [WBC] 05, all polymorphs, protein 36 mg/dl, sugar 86mg/dl). Pan-viral panel (*Flavivirus*, *Enterovirus*, paramyxovirus, and herpesvirus), protein 14-3-3, and malignant cytology of CSF were negative.

Outcome and follow-up

She was managed with antiepileptic drugs (AEDs) according to status epilepticus protocol. Her sensorium completely improved and she was extubated. Repeat MRI brain after 5 days showed the persistence of pulvinar and thalamic hyperintensities and serials EEGs done showed the presence of periodic lateralized epileptiform discharges (PLEDs) despite clinical improvement.

Among the paraneoplastic panel (antiamphiphysin, anti-Ri, anti-Hu, anti-Yo, and PNMA 2), her anti-Ri-ANNA2 antibody (specific for mammary/lung CA) was found to be positive. Considering the history of CA breast, a detailed oncological evaluation was done but no mass lesions or palpable lymph nodes were found. Whole-body

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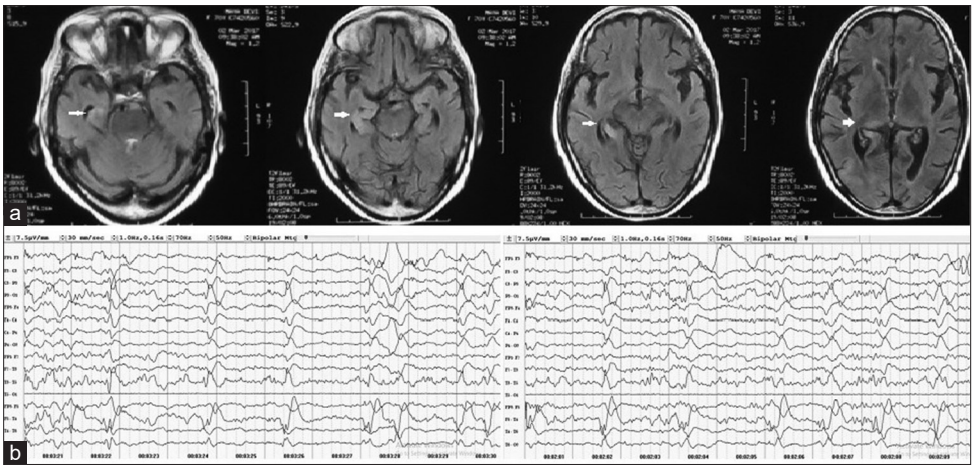

Figure 1: (a) Magnetic resonance imaging of the brain demonstrates T2-fluid attenuated inversion recovery hyperintensity in the right temporoparietal, right thalamic, and pulvinar areas. (b) Electroencephalography showing right temporal spikes with intermittent attenuation of background

positron emission tomography scan was also normal. In view of paraneoplastic encephalitis, she was initiated on immunotherapy with intravenous immunoglobulins (IVIg), with an initial short course given over 5 days (total 75 gms) followed by fortnightly IVIg.

She showed subsequent clinical and radiological improvement and continued to be symptom free for the next 1½ months but presented again with staring spells and left upper limb epilepsia partialis continua (EPC). MRI brain revealed persistent pulvinar hyperintensities, and EEG again showed bilateral PLEDs. She was managed with AEDs, but when EPC persisted, she was intubated and managed with midazolam infusion. In view of the recurrence of symptoms on IVIg, she was given methylprednisolone and initiated on weekly rituximab injections. She again improved gradually and remained asymptomatic for 3 weeks following which she was readmitted in deeply comatose state with recurrence of symptoms. CSF was repeated and this time showed five WBCs (all lymphocytes, sugar 76, and protein 27). CSF smear revealed larvae of SS [Figure 2a], which were also seen in sputum and stool as well [Figure 2b and c].

She was started on ivermectin 200 μg/kg/day along with albendazole 400 mg BD × 14 days. Rituximab was stopped, steroids were tapered, and CD19 levels were monitored. Her sensorium gradually improved over 1 month, after starting treatment and she was discharged. She has remained stable after starting treatment and presently is able to walk with a walker.

Case 2

RK, a 60-year-old male, with chronic kidney disease on biweekly hemodialysis, with recent herpes zoster ophthalmicus, presented with complaints of intractable left periorbital and hemicranial pain. Clinical examination revealed residual herpetic lesions over the V2 segment of trigeminal nerve distribution and C2 dermatomes. He was initially managed as a case of postherpetic neuralgia with carbamazepine, but his headache failed to respond, and his sensorium gradually worsened. He became drowsy and disoriented and was noted to develop left third nerve palsy. There was no focal motor weakness or sensory deficit; reflexes were present in the upper limbs but diminished in the lower limbs, and plantars were bilaterally flexor.

Investigations

MRI brain was done keeping a clinical suspicion of herpes encephalitis but was essentially normal except for bulky bilateral orbital nerves. CSF analysis revealed high opening pressures with ten lymphocytes, raised protein, and near normal sugars.

Outcome and follow-up

He was started on injectable acyclovir at renal adjusted doses, which he received for a total of 2 weeks. His sensorium continued to worsen, and he became restless and irritable and developed EPC of the left upper limb. EEG revealed generalized slowing. Serial ABGs and other laboratory parameters yielded no metabolic derangements attributable to his symptoms.

In view of rapid progression of symptoms, a repeat CSF was done 7 days after initiation of acyclovir which showed nil cytology but persistently high protein. CSF for autoimmune/paraneoplastic encephalitis antibodies and 14-3-3 protein was negative. CSF smear revealed larvae of strongyloides and observed under direct visualization [Figure 3]. Tuberculosis polymerase chain reaction, cryptococcal antigen, and KOH/India ink preparation were negative. He was started on ivermectin at the recommended dose of 200ug/kg/day along with albendazole at 400 mg twice daily regimen. Stool culture was also positive for larvae of SS. The patient showed dramatic improvement with treatment with complete neurological recovery.

Discussion

The Indian subcontinent is endemic for SS, and it usually presents as a benign gastrointestinal illness with most patients being either asymptomatic or reporting occasional epigastric discomfort. In a study on 78 asymptomatic individuals from southern India, the prevalence of parasitic infections was

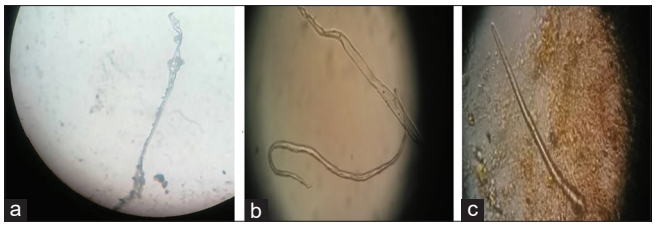

Figure 2: (a) Larvae of *Strongyloides stercoralis* seen in wet mount preparation of cerebrospinal fluid. (b) Wet mount preparation of sputum showing larvae of *Strongyloides stercoralis.* (c) Wet mount preparation in stool revealing larva of *Strongyloides stercoralis*

reported as 97.4%, with 20% constituting for strongyloides infection. Similarly, in another community-based study from Assam, 17 (8.5%) of the total 198 patients were found to be infected with strongyloides.[5,6]

In the classic life cycle, the female SS nematode travels from the skin to the lungs and then to the gastrointestinal tract of its host. The characteristic feature of autoinfection, a phenomenon by which larvae reproduce in the gut of the host itself and re-enter circulation, can result in overwhelmingly high parasite burden and has been termed hyperinfection. When this increased parasite load disseminates into areas outside the traditional life cycle, with spread into skin, liver, brain, and meninges, it is termed disseminated strongyloidiasis.

Patients with impaired cellular immunity, like those with hematological malignancies, posttransplant patients, and patients on long-term steroids like both our patients have a predilection for hyperinfection and/or dissemination.[7] The recent increase in the use of corticosteroids has shown an increase in the incidence of hyperinfection/dissemination, especially in the immunocompromised host and unless recognized and treated early, and it has a high mortality of 15%–87%.[8]

SS with dissemination into the CSF may present with varying symptoms such as altered neurological status, seizures, or headache. Very few cases of SS meningoencephalitis have been reported in literature and most of the cases were diagnosed postmortem.[3] We found only two cases where SS dissemination into the CSF was diagnosed antemortem, and in both instances, the patients were unsalvageable.[3,4] To the best of our knowledge, no cases with cerebral or meningeal dissemination with SS have been reported from India. We report two patients, both with underlying immunosuppression who presented with seizures, altered mentation, and worsening neurological status; in whom, direct visualization of the SS nematode in the CSF cinched the diagnosis of disseminated SS.

Disseminated SS can be highly fatal if not treated; hence, timely diagnosis and prompt management is crucial to salvaging the patient. In a highly endemic country like India, in patients with suspected meningoencephalitis unresponsive to antimicrobials, we recommend that a high index of suspicion should be maintained for disseminated cerebral SS

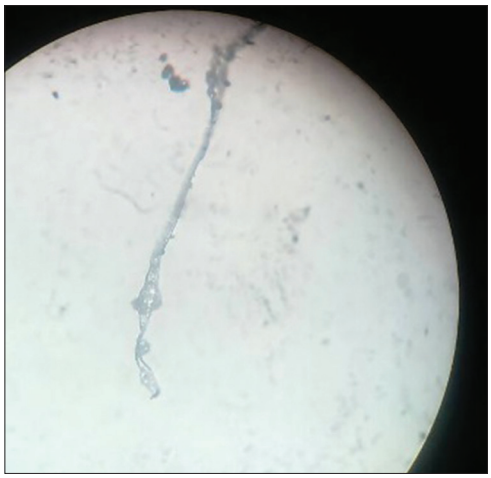

Figure 3: Cerebrospinal fluid smear showing larvae of *Strongyloides stercoralis* on direct microscopic visualization

and routine screening of the same should be done, especially if they are immunocompromised or have been on long-term steroids.

There is no one ideal screening or diagnostic test for strongyloidiasis, making it a difficult infection to detect in humans. The most reliable method for the diagnosis of strongyloidiasis is by observing strongyloid larvae in stool or sputum specimens, but due to fluctuation in the rate of larval excretion, especially in stools, it may not always be accurate, and multiple stool samples require to be tested.[9] Peripheral eosinophilia may be seen in 50%–80% of the infected patients, but in patients on concomitant steroids, eosinophilia may not be a reliable marker as was the case in our first patient. In suspected dissemination into CSF, direct visualization of a wet mount preparation of CSF can reveal the presence of these rhabditiform larvae, as was seen in our patients.

Albendazole, mebendazole, and thiabendazole have all been found beneficial in the treatment of SS, but ivermectin has emerged as the treatment of choice at a recommended dose of 200ug/kg/day for 7 days for uncomplicated SS[10]

In hyperinfection and dissemination, it should be continued at the same dose for at least 2 weeks till stool samples are found negative for strongyloides. Monitoring the effect of treatment is difficult due to fluctuations in the rate of parasite excretion, especially in stool.

Strongyloidiasis is a nematode infection with a tendency to become chronic with fatal complications of hyperinfection syndrome and disseminated infection along with a host of other potential complications such as Gram-negative bacteremia and meningitis. As the infection is mostly chronic and asymptomatic and there is no specific ideal test to diagnose the disease, it still tends to be a diagnostically elusive disease even in the present era.

As most cases of hyperinfection syndrome and disseminated strongyloidiasis happen in immunocompromised individuals,

especially those who are taking systemic steroids, physicians in the endemic areas should be aware of the bizarre manifestations of the disease that can mimic other diseases leading to misdiagnosis and medical errors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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