Triple Whammy! Steroids, Strongyloidiasis and Septic Meningitis

Sir,

Strongyloidiasis is an intestinal nematode that can cause a spectrum of manifestations, ranging from asymptomatic eosinophilia in the immunocompetent to hyperinfection syndromes in immunocompromised hosts that may be associated with severe sepsis and death. The latter typically affect individuals with deficient cell-mediated immunity including patients on long-term steroids, cytotoxic drugs, Human T-cell lymphotropic virus (HTLV)-1 infection, Human Immunodeficiency Virus (HIV) infection, chronic alcohol use and chronic liver disease.[1] Strongyloidiasis is known to be associated with disseminated bacterial infections, including bacteremia, pneumonia and meningitis, most commonly due to gram-negative organisms that colonize the bowel.[2] We highlight, through this report, the necessity to screen for strongyloidiasis in a susceptible patient who presents with gram-negative meningitis.

A 25-year-old male presented to an outside hospital with ascending hypoesthesia over bilateral lower limbs for 1 year, superimposed on which he developed discrete, erythematous nodules over his lower limbs for 1 week. He was initiated on multidrug therapy (MDT) for multibacillary Hansen's disease along with steroids (oral prednisolone 10 mg twice daily), which he continued for almost 1 year. Slit-skin smears or skin/nerve biopsy were not performed. He presented to our center with 1 month of fever, headache and altered sensorium, as well as upper abdominal pain with vomiting. On examination, he was febrile but hemodynamically stable. He was pale and had a cushingoid habitus. Skin examination revealed nodular lesions over the thighs, along with desquamation of skin of both lower limbs. He was confused, had neck stiffness and bilateral extensor plantar response. The fundus examination was normal. He also had bilaterally thickened ulnar and greater auricular nerves [Figure 1].

Investigations revealed total leucocyte count 55,100 cells/mm^3 with differential count of 10% myelocytes, 75% neutrophils, 6% eosinophils, 1% monocytes and 8% lymphocytes. Contrast-enhanced CT brain was normal. Cerebrospinal fluid (CSF) analysis revealed turbid appearing fluid with glucose of less than 5 mg/dL (concomitant blood sugar

105 mg/dL), protein 68 mg% and CSF cell count of 22,650 cells/cu.mm (92% neutrophils and 8% lymphocytes). CSF smear showed abundant pus cells but no bacteria or atypical cells. CSF aerobic culture grew extended spectrum beta lactamase (ESBL) *Escherichia coli* (*E. coli*). CSF for fungal smear, India ink, Ziehl-Neelsen stain for acid fast bacilli (AFB), Gene Xpert for tuberculosis was negative. HIV serology was negative. Blood culture did not grow any organism. Hepatic and renal function and blood sugar were within normal limits. Nerve conduction studies were suggestive of mononeuritis multiplex. He was treated with meropenem 2 g intravenously every 6 hours for 21 days. Lumbar puncture was repeated on 10th day, which showed an improvement in CSF appearance and cell counts (312 cells/cu.mm). In view of persistent epigastric pain and vomiting, endoscopy was performed which revealed Strongyloides stercoralis infestation. The gastric mucosal biopsy also showed Strongyloides stercoralis infestation [Figure 2]. Slit skin smear showed broken AFB. Skin biopsy from the thigh region showed Borderline Lepromatous disease with leukocytoclastic vasculitis consistent with erythema nodosum leprosum (ENL)**.** For strongyloidiasis, he was treated with oral ivermectin (200 mcg/kg) for 5 days in view of probable strongyloides hyperinfection. ENL was managed via MDT for Hansen's disease with high dose clofazimine (100 mg thrice daily). He improved rapidly in terms of sensorium, vomiting and skin lesions with these measures.

Strongyloidiasis is a definite albeit uncommon risk factor for gram-negative meningitis, accounting for up to 7% of the cases.[3] The mechanism is believed to be multifold. This may involve disruption of the gastrointestinal mucosa by the parasite followed by direct entry of bowel flora into the bloodstream. Through a piggyback mechanism, bowel flora may adhere to the parasite as it migrates. A third mechanism is an excretion from the alimentary tract of the parasite into the blood during migration.[4] The organisms hence implicated in bacteremic illnesses are mostly gram-negative although gram-positive organisms have also been reported.[5] Drug-resistant ESBL *E. coli* meningitis is highly uncommon in association with strongyloidiasis with only two other fatal cases reported in the literature and ours being the third who recovered [Table 1].

Strongyloidiasis treatment for hyperinfection necessitates ivermectin for five days, followed by documentation of negative stool examination for parasites, else therapy needs to be extended.[8] Gram-negative meningitis requires a different therapeutic paradigm compared to the usual acute pyogenic meningitis. Steroids are of no

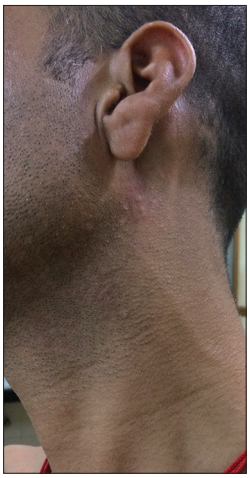

Figure 1: Enlargement of the greater auricular nerve seen along with nodular infiltration below the earlobe

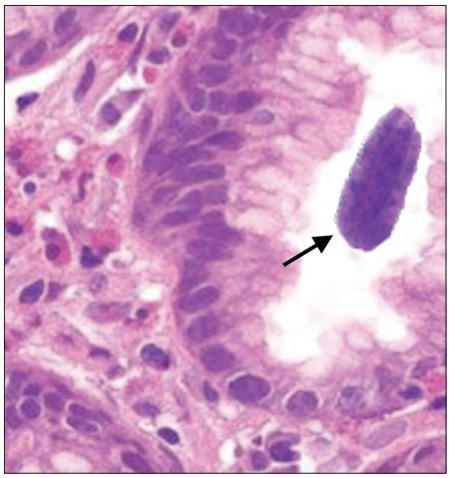

Figure 2: Gastric mucosal biopsy showing a section of adult Strongyloides stercoralis worm (arrow) (Hematoxylin and Eosin × 400)

Table 1: Reports in the literature of ESBL *E. coli* meningitis in association with strongyloidiasis

Author/ Year	Age / Gender of patient	Underlying condition	Outcome
Gomez *et al*./ 2013[6]	43/ male	Prednisolone used for Bell's palsy Travel to an endemic region	The patient died due to severe gram-negative sepsis and septic shock
Dahal *et al*./ 2017[7]	59/ female	Diabetes, rheumatoid arthritis on methotrexate, abatacept and prednisolone	Unique drug resistance pattern: *E. coli* (CSF cultures) sensitive to ceftriaxone but resistant to piperacillin-tazobactam The patient died due to multi-organ dysfunction, and severe meningitis
Present case	25/male	Chronic steroid therapy for lepra reaction	Patient recovered after prolonged antibiotic therapy

benefit in this setting and may be associated with harm. The duration of therapy is unclear.[9] However, patients should be treated for at least 3 weeks due to the risk of relapse with shorter courses, with repeat analysis of the CSF after 5-7 days. Cultures can remain positive for prolonged periods despite clinical improvement and warrant extension of therapy for 10-14 days beyond the last positive culture. The identification of concomitant strongyloidiasis in gram-negative or culture-negative meningitis is also relevant because these patients have been reported to develop recurrent meningitis.[1,10-12] In our patient, steroids for lepra reaction enhanced susceptibility to strongyloidiasis which, in turn, provided a pathway for gram-negative meningitis.

There were two additional points of interest in our patient. The first is that despite severe bacterial meningitis, he presented with a subacute duration of illness. This may be due to ongoing steroid therapy that may have suppressed acute presentation. Culture-negative meningitis is more common in association with strongyloidiasis. The second is the occurrence of multidrug-resistant meningitis from the community, likely due to the unfortunately widely prevalent culture of empirical antibiotic therapy practiced in our country.

This case highlights the need to search for strongyloidiasis infection as a possible nidus in patients who present with gram-negative meningitis. It also triggers considerations for secondary prophylaxis for strongyloidiasis in patients who have ongoing immunosuppression for various neurological conditions.

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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