CASE REPORT

Meningitis due to scrub typhus: the importance of a differential diagnosis in an endemic area

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SUMMARY

A patient with fever and neck stiffness was treated as partially treated bacterial meningitis based on history, examination and cerebrospinal fluid analysis. After initial improvement with ceftriaxone, vancomycin and dexamethasone, symptoms recurred. Fever resolved promptly after treatment was started with doxycycline, when scrub typhus immunoglobulin M test came positive. Meningitis is a well-known complication of scrub typhus. However, scrub typhus is seldom considered in the differential diagnosis of meningitis in the Indian subcontinent. Early diagnosis and prompt institution of doxycycline therapy may lead to early cure of scrub typhus even when features of meningitis supervene. However, ceftriaxone which is commonly used to treat bacterial meningitis is suboptimal in the treatment of scrub typhus.

BACKGROUND

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium. It is transmitted to humans by bite of infected larvae of trombiculid mites (chiggers). This disease is endemic in many countries in South Asia, including Nepal. This is generally an easily treatable condition, doxycycline being the drug of choice that leads to prompt therapeutic response. Though vaccines are not available, it can be prevented with chemoprophylaxis with tetracycline or chloramphenicol and mite control measures like insect repellents and miticides.¹

Scrub typhus has been a re-emerging health problem in Nepal, with outbreaks being recorded after the devastating earthquake in 2015.² It is one of the neglected and under-reported tropical diseases in the subcontinent including Nepal.³

Scrub typhus ranges from a mild disease with fever, eschar, rashes, lymphadenopathy, headache, myalgia, cough, gastrointestinal symptoms to a fatal illness with acute respiratory distress, meningoencephalitis, gastrointestinal bleeding, acute renal failure, hypotensive shock and coagulopathy.⁴

Many cases of scrub typhus associated with meningitis or meningoencephalitis have been reported.^{5 6} During acute encephalitis syndrome (AES) outbreak in Gorakhpur, Uttar Pradesh, India, in 2015, investigations showed scrub typhus immunoglobulin (Ig)M in >60% cases.⁷ Similarly, another study done in 2016 in Gorakhpur also indicated a role for scrub typhus in the aetiology of AES.⁸ We report a case from Patan Hospital, Nepal, first treated as bacterial meningitis,

which later turned out to be scrub typhus. The objective of our case report is to sensitise the readers to keep scrub typhus in the differential diagnosis in patients with meningitis, in scrub typhus endemic areas like Nepal and more importantly to emphasise the fact that ceftriaxone, the commonly used drug for bacterial meningitis, is suboptimal therapy for typhus for which the drug of choice is doxycycline.⁹

CASE PRESENTATION

A 24-year-old woman from Sindhupalchowk district in eastern Nepal presented in our emergency department with complaints of fever for 8 days, which was high grade, continuous and without chills and rigour. It was associated with pain in the back of her neck, but no headache, vomiting, dizziness, vision difficulty, altered mentation, cough, chest pain, abdominal pain, burning urine, any form of rash or eschar. She had taken cefixime tablets prescribed by the local pharmacy in Sindhupalchowk for 3 days, but without any improvement.

Subsequently, she went to a private hospital in Kathmandu, where meningitis was suspected due to the presence of neck stiffness with fever. Cerebrospinal fluid (CSF) analysis was done, where a diagnosis of meningitis was made but due to financial constraints, she came to Patan Hospital.

INVESTIGATIONS

Complete blood count: white cell count (WCC) $7.8 \times 10^9/L$; neutrophils (N) 60%; lymphocytes (L) 37%; monocytes (M) 3%; red blood cells (RBC) $3.7 \times 10^{12}/L$; haemoglobin 11 g/dL; platelets $191 \times 10^9/L$; random blood sugar 99 mg/dL; urea 19 mg/dL; creatinine 0.6 mg/dL; sodium 135 mmol/L and potassium 3.7 mmol/L.

Hepatic panel: bilirubin total 1 mg/dL and direct 0.4 mg/dL; alanine transaminase 30 units/L; aspartate transaminase 38 units/L; alkaline phosphatase 88 IU/L.

CSF analysis: RBC 50 cells/ μL , WCC 90 cells/ μL ; N 66%; L 34%; protein 124 mg/dL, sugar 51 mg/dL, culture/sensitivity (C/S) no growth.

CSF adenosine deaminase (ADA) and acid fast bacillus staining (AFB) were not done.

DIFFERENTIAL DIAGNOSIS

Working diagnosis was partially treated bacterial meningitis based on the CSF findings.

The main differential diagnosis was tubercular meningitis due to longer duration of fever and mild CSF pleocytosis with high protein.

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TREATMENT

Treatment was started with intravenous ceftriaxone and vancomycin. Intravenous dexamethasone was given for the initial 5 days and then stopped with the continuation of the antibiotics.

OUTCOME AND FOLLOW-UP

She improved initially with resolution of fever; however, she again started to have fever spikes with headache and neck stiffness after withdrawing dexamethasone on sixth day, while she was still on both ceftriaxone and vancomycin.

We decided to do a repeat spinal tap especially to try to rule out tubercular meningitis, and at the same time, we also sent blood for serology for scrub typhus, brucella, leptospira, malaria and dengue.

Repeat CSF showed a normal picture despite the patient worsening (RBC nil; WCC 2 cells/ μ L; N 0%; L 2%; protein 40 mg/dL; sugar 47 mg/dL; ADA 3 U/L; AFB nil; C/S no growth). Brucella, leptospira, malaria and dengue serology was negative.

Then we added doxycycline 100 mg tablet twice daily. Fever promptly resolved the next day. After about 3 days, scrub typhus IgM came positive by InBios Scrub Typhus Detect IgM ELISA. Further diagnostic tests like CSF PCR for scrub typhus and tuberculosis were not done due to financial constraints.

We then stopped ceftriaxone and vancomycin and discharged her with doxycycline. On follow-up after 4 days, she was well with complete absence of fever.

DISCUSSION

Acute meningitis is a medical emergency requiring prompt evaluation and management. Scrub typhus is an acute febrile illness that can manifest as meningitis or meningoencephalitis, in about one-fifth of patients.¹⁰ In one study from India, meningoencephalitis was the most common complication of scrub typhus, followed by pneumonia.¹¹

The clinical and laboratory features differentiating scrub typhus meningitis from other usual forms of meningitis have been studied and reported. Scrub meningitis has longer duration of fever prior to presentation than bacterial meningitis. CSF analysis of patients with scrub typhus have significantly less pleocytosis, greater lymphocyte proportion and a lesser degree of protein elevation than in cases of bacterial meningitis.¹⁰

Similarly, scrub typhus can be differentiated from tubercular meningitis by lesser duration of symptoms, lesser CSF pleocytosis and protein and lesser CSF ADA, but these are all relative estimations.⁶

We diagnosed scrub typhus in our patient using InBios Scrub Typhus Detect IgM ELISA, which has sensitivity of 93% and specificity of 91%.¹² Hence, positive predictive value of the test for scrub typhus will be higher in an endemic country like Nepal. Endemicity of scrub typhus in Nepal, positivity in serum by IgM ELISA and prompt therapeutic response to doxycycline pointed to the diagnosis of scrub typhus, even without doing confirmatory molecular tests like PCR which financially would not have been possible even if the test was available.

The surprising feature was how the CSF picture normalised without the use of proper antibiotics. But the spontaneous clearing of CSF pleocytosis in scrub typhus has been noted in a study in South Korea in 1997,¹³ and a study done in India in 2005–2011 has also shown gradual decrement in CSF pleocytosis and protein level over time.¹⁴

During the first 5 days of treatment, she was treated with ineffective antibiotics and dexamethasone. At least in mice,

dexamethasone does not seem to induce the growth of *O. tsutsugamushi*.¹⁵ Though not validated, some studies have shown positive effects of corticosteroid in rickettsial disease.^{16 17} Crucially, it is important to note that typhus infections in general will not respond to ceftriaxone which is commonly used for bacterial meningitis as in our case.⁹

Learning points

- Scrub typhus is an acute febrile illness ranging from a mild disease to a fatal illness including meningitis.
- Scrub typhus should be considered in the differential in any case manifesting as meningitis, in scrub typhus endemic region.
- Scrub typhus meningitis, if promptly treated may respond well to doxycycline but not to ceftriaxone, the commonly used drug to treat bacterial meningitis.

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