

<p>TITLE OF CASE <i>Do not include "a case report"</i></p>
<p>Scrub typhus meningitis: the importance of a differential diagnosis in an endemic area (Meningitis due to scrub typhus: the importance of a differential diagnosis in an endemic area)</p>
<p>SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i></p>
<p>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 IgM 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.</p>
<p>BACKGROUND <i>Why you think this case is important – why did you write it up?</i></p>
<p>Scrub typhus is an acute febrile illness caused by <i>Orrencia tsutsugumashi</i>, 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.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 IgM in > 60% cases⁷ and similarly, another study done in 2016 in Gorakhpur also indicated a role for scrub typhus in the etiology of AES.⁸ We report a case from Patan Hospital, Nepal, first treated as bacterial meningitis, that (later) turned out to be scrub typhus. The objective of our case reporting is to sensitize 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 emphasize the fact that ceftriaxone, the commonly used drug for bacterial meningitis, is suboptimal therapy for typhus⁹ for which the drug of choice is doxycycline.</p>
<p>CASE PRESENTATION <i>Presenting features, medical/social/family history</i></p>
<p>A 24 year female from Sindhupalchowk district in eastern Nepal presented in our emergency department with complains of fever for 8 days, which was high grade, continuous, and without chills and rigor. 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 or burning urine. 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 presence of neck stiffness with fever. Cerebrospinal fluid (CSF) analysis was done,</p>

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where a diagnosis of meningitis was made but (for financial reasons) , she came to Patan Hospital.

INVESTIGATIONS *If relevant*

CSF analysis-(mention with units)-Red Blood Cell (RBC)- 50, White Blood Cell (WBC)- 90, Neutrophil (N)-66 Lymphocyte (L)-34, Protein- 124, Sugar- 51, Culture/Sensitivity (C/S)- no growth
CSF Adenosine Deaminase (ADA), Acid Fast Bacillus staining (AFB) were not done.

Other labs

DIFFERENTIAL DIAGNOSIS *If relevant*

Working diagnosis was partially treated bacterial meningitis based on the CSF findings. The main differential diagnosis was tubercular meningitis.

TREATMENT *If relevant*

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 5 days 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 following results-

RBC- nil, WBC- 2, NOL2, Protein- 40, Sugar- 47, ADA- 3, AFB- nil, C/S- no growth
Brucella, leptospira, malaria, dengue serology- 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. 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 *Include a very brief review of similar published cases*

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

We treated this patient initially as partially treated bacterial meningitis because she had neck stiffness and the CSF findings suggested meningitis, but we did not know what kind (Rewrite).. Tubercular meningitis was our differential diagnosis from the very beginning owing to longer

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duration of fever and mild CSF pleocytosis with high protein. After the patient started to develop fever and headache following dexamethasone withdrawal, we repeated CSF analysis. But it was surprising to get a normal CSF picture despite the patient was worsening. We also sent blood for scrub typhus, brucella, leptospira, malaria and dengue, and simultaneously added doxycycline, which promptly cleared her fever the next day. Later, scrub typhus IgM came positive, which was done by InBios Scrub Typhus Detect IgM ELISA. It 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.

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 scrub typhus patients 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

The surprising feature was how the CSF picture normalised without the use of proper antibiotics. In CSF leucocyte and protein influx, there is important role of matrix metalloproteinase, especially MMP 9. Studies have shown that the use of dexamethasone decreases the activity of MMP 9. By this mechanism, it plays role in reducing CSF pressure and therefore it is beneficial in cases of meningitis. Reduction in MMP 9 activity also helps in early normalisation of CSF picture.¹³ During first five days of treatment, we treated her with ineffective antibiotics and dexamethasone. But the good news is that at least in mice, dexamethasone does not seem to have effect on the growth of *O. tsutsugumashi*.¹⁴ Finally 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/TAKE HOME MESSAGES *3 to 5 bullet points – this is a required field*

- 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 can be differentiated from bacterial and tubercular meningitis with various clinical and CSF parameters.
- Scrub typhus meningitis, if promptly treated may respond well to doxycycline but not to ceftriaxone, the commonly used drug to treat bacterial meningitis.

REFERENCES *Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)*

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FIGURE/VIDEO CAPTIONS *figures should NOT be embedded in this document*

PATIENT'S PERSPECTIVE *Optional but strongly encouraged – this has to be written by the patient or next of kin*

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