Spotted fever rickettsiae and tuberculous meningitis dual infection presenting as acute encephalitis syndrome: A fatal case report

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Both spotted fever group rickettsiae (SFGR) and tuberculous meningitis (TBM) are associated with high morbidity and mortality in the absence of timely diagnosis and appropriate treatment. Simultaneous infections by SFGR and TBM may not be surprising in regions where both the infections may be prevalent. However, reports on co-infection with SFGR and tuberculosis (TB) are not available in literature/previous studies. This is the first case reporting of dual infection of spotted fever rickettsiae with *Mycobacterium tuberculosis*. The probability of dual infection could possibly hamper the recovery of a patient after treatment, especially in case when any one of these remains undiagnosed and untreated. Thus, careful monitoring for dual exposure for such infections in case of suspicion is very important for initiating effective and quick treatment. Here, we report a fatal case of dual infection caused by SFGR and meningeal TB in a 19-yr-old patient presenting as acute encephalitis syndrome.

Case Report

A 19-yr-old male patient presenting with a seven-day history of high grade fever, myalgia and headache was admitted to the Assam Medical College and Hospital (AMCH), Dibrugarh. On day of admission, he had multiple seizures and developed altered sensorium. On examination, the patient was febrile at 103 °F; had tachycardia of 104/min; and two eschars were noted on left forearm and opisthenar, each measuring between 0.1 and 0.3 cm diam (Figs. 1a and b). Total leukocyte count, erythrocyte sedimentation rate, serum sodium (Na⁺), serum potassium (K⁺), blood urea nitrogen, haemoglobin, urea and creatinine estimation readings were 1.12 × 10⁹/l, 18 mm at the end of first hour (AEFH), 124.5 mmol/l, 4.95 mmol/l, 11.64 mmol/l, 120 g/l, 1.62 mmol/l and 79.56 µmol/l, respectively. Initially, the patient was managed as per acute encephalitis syndrome (AES) protocol at the Department of Medicine, AMCH, Dibrugarh. Ceftriaxone, mannitol and anti-epileptic drugs were administered. The patient was advised for magnetic resonance imaging (MRI) with magnetic resonance spectroscopy (MRS) of the brain, but the patient declined it. Based on typical presence of eschar and subsequent laboratory findings (presence of antibodies against SFGR), treatment was supplemented with 100 mg doxycycline twice daily. The patient had a dramatic recovery within two days of treatment. He was discharged from hospital on the Day 6 post-admission with a prescription of doxycycline 100 mg twice daily for two weeks. Two days after discharge, the patient again returned to the hospital in a semi-conscious state and was readmitted. On examination, the patient showed signs of shock and aspiration pneumonia. There was history suggestive of multiple seizures. Subsequent cerebrospinal fluid (CSF) analysis showed protein: 0.75 g/l, sugar: 0.4 g/l and total cell count: 50 cells/µl; of which lymphocytes and polymorphonuclears accounted for 60 and 40% respectively, and adenosine deaminase (ADA) was recorded as 14.7 IU/L. Basic resuscitative care was given, but the patient failed to respond and expired within 24 h.
DISCUSSION

Development of eschar represents one of the characteristic features of human rickettsial infection, although mere presence of an eschar does not seem to be a hallmark of rickettsial diseases. Serology and molecular confirmation thus, remains the gold standard for rickettsial diagnosis. The clinical presentation in SFGR varies from remaining clinically mild to severely fatal outcome, often resembling other infections. Haematological test of the patient revealed elevated leukocyte count, low sodium and high urea content. Studies have reported hyponatraemia and abnormalities in white blood cell count as typical clinical findings of SFGR. Serological test of the patient’s sera showed antibodies against SFG Rickettsia conorii antigen which was further confirmed by PCR (Fig. 2a). PCR was performed using the primers R17k-M61F-ACCTTACAAATTCTAAAAACCATTACT, R17K31F-GCTCTTGCAGCTTCTATGTTACA and Rr2608R-CATTGTCCGTCAGGTTGGCG designed to amplify a 434 bp fragment of 17 kDa outer membrane antigen gene of Rickettsia genus. Accordingly, doxycycline was added to his medication. Doxycycline has been the appropriate drug for treating rickettsial infections. However, in our case, initial recovery on treatment with doxycycline followed by a sudden health deterioration requiring re-hospitalization along with the CSF findings led to a suspicion of some other infection.

In the patient’s second episode of hospital admission, the CSF analysis was suggestive for meningeal TB. Thus, PCR from CSF filtrates was performed using primers TB-devRf3-ATCTGTGTGCCGCATGCC and TB-devRr3-GTCCAGCGCCCACATCTTT designed to amplify a 162-bp fragment of 16S rRNA gene. Interestingly, in this case, PCR amplification revealed the presence of M. tuberculosis in CSF filtrates (Fig. 2b). But unfortunately, prior to any treatment with anti-tubercular drugs, the patient expired. The patient was advised for MR imaging with MRS of the brain at his first admission, which might have picked up CNS-TB. But the patient had declined further investigations and was discharged on request following the positive clinical response to doxycycline.

Seroepidemiological surveys on rickettsial diseases have demonstrated the circulation of SFGR in Northeast region (NER) of India. TB has also been a major public health concern in the NER of India, especially in remote areas. This report demonstrated that the patient had acquired both SFGR and TBM. Possibly there was Immune Reconstitution Syndrome after treatment for the Rickettsial infection which might have unmasked the CNS-TB. Immuno pathogenesis of TB involves the driving force of matrix metalloproteinase (MMP), an enzyme involved in extracellular matrix destruction. Previous studies have shown increased expression of MMPs activity in CNS-TB. On the other hand, doxycycline has been reported to be the only licensed MMP inhibitor drug available which has the potential to suppress MMP activity in TB infection globally. So, when doxycycline was included in the medication of the patient, it should have been effective against CNS-TB based on the previous findings of an in vitro study. However, considering the fact that CNS-TB is one of the devastating forms of TB associated with a high rate of mortality, its recovery mainly depends on the phase of infection at which treatment was started. Moreover, the increase in multidrug and new drug resistant TB is increasing the concern. Some studies have also reported bacterial superinfection to be one of the leading causes of death in TB cases. However, in this case, there remains an enigma of whether superinfection was caused by Rickettsia over TB or vice versa. This being a single case, could not provide a clear picture of the exact time period of exposure to both these agents. Further studies with regard to capability of doxycycline, as a potent inhibitor of MMP and its effectiveness in treating coinfection of TB and other aetiologies remains to be explored.

Hence, the findings indicate that rickettsial infection might have the potential to exacerbate tuberculosis infection, posing a new challenge to clinicians. It is also of immense need to consider rickettsial diseases as another important etiological agent of unidentified fever cases in Northeast India, which has the potential of worsening health system in TB endemic regions. The probability of coinfection with >1 infectious agent should be considered especially in a region which might be hyper-endemic for these agents.
Conflict of interest: None.

Ethical approval: Written consent was obtained from the patient’s next kin (as the patient was in an unstable state at the time of sample collection).

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REFERENCES


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