CASE REPORT

Rare and Unusual Presentation as Immune Thrombocytopenic Purpura in Scrub Typhus Complicated by Meningitis and Acute Kidney Injury

Prawash Kumar Chowdhary[1], Rakesh Kumar Agrawal[2], Sanjeev Kumar[3], Sanjeev Anant Kale[4], Vishal Kumar[5]

Abstract

Scrub typhus is a known etiology of acute febrile illness in tropical regions such as Asia–Pacific. Several such reports are from the Indian subcontinent with manifestations such as non-specific febrile illness or multiorgan dysfunction [Acute respiratory distress syndrome (ARDS), myocarditis, hepatitis, acute kidney injury, or meningoencephalitis]. We came across a case with a presentation as immune thrombocytopenic purpura complicated by meningitis and acute kidney injury secondary to scrub typhus. This combination of presentation is rare and demands meticulous clinical examination and targeted management toward scrub typhus.

Keywords: Immune thrombocytopenic purpura, Meningoencephalitis, Scrub typhus.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24256

Introduction

Scrub typhus is an acute infectious rickettsial infection caused by *Orientia tsutsugamushi*, a gram-negative coccobacillus.[1] Infected trombiculid chigger mites transmit this organism (especially, *Leptotrombidium deliense*), found in semi-arid regions of heavy scrub vegetation. Scrub typhus is a zoonotic disease with humans being accidental hosts. The term "scrub" refers to vegetation (terrain between woods and clearings) that harbors the vector. However, it is endemic in the Asia–Pacific region but has a worldwide distribution. The rickettsial disease has been documented in India since the 1930s, with the initial reports being from the Kumaon region.[2] It gained notoriety only during the Second World War when it caused several epidemics among the troops with resulting mortality and morbidity.[3,4]

Scrub typhus often presents with fever, a maculopapular rash with an eschar at the mite-bite site, myalgia, hepatosplenomegaly, and in severe cases with acute lung injury, acute kidney injury, and multiorgan dysfunction.[5] The case fatality rate ranges from 30 to 50%.[6] Thrombocytopenia and neurological involvement is a prominent feature of this disease.

Here we describe a case of scrub typhus with rare presentation as immune thrombocytopenic purpura complicated by meningitis and acute kidney injury. There are only limited case reports with such a combination. The Institutional Ethics Board approved the study.

Case Description

A 37-year-old male was presented with acute onset fever, myalgia, headache, and generalized weakness for 10 days. He was a chronic alcoholic without any other comorbidity. One week before the onset, he went on vacation in a hilly forest area. On clinical examination, he was conscious and oriented. His blood pressure was 82/56 mm Hg with tachycardia of 126/minutes and tachypnea of rate 26/minutes. He was febrile (101°C). There was no pallor or lymphadenopathy, but icterus and pedal edema were present. Chest auscultation revealed bibasilar crepitations. The systemic search showed an eschar on the left scrotum.

Based on clinical suspicion of scrub typhus, started administration of Doxycycline 200 mg once a day with supportive measures. In the next 2 days, he had deterioration of mental and respiratory status. He was put on non-invasive ventilation with bi-level positive airway pressure (BiPAP). Intravenous azithromycin 500 mg once a day added. Both the Weil–Felix test and Scrub typhus antibody test were positive, having significant titers. Gradually, the respiratory status improved but the patient remained drowsy. Neurological examination showed neck stiffness with normal optic fundus. T1 contrast MRI revealed leptomeningeal enhancement (Fig. 1), and fluid-attenuated inversion recovery (FLAIR) images showed diffuse thickening along with the bilateral temporoparietal areas (Fig. 2). Thrombocytopenia of 9,000/mm^3 did not permit cerebrospinal fluid (CSF) access. A bone marrow study revealed megakaryocytic hyperplasia (Figs 3 to 5). The antinuclear antibody (ANA) was found negative. One unit

[1,4]Department of Nephrology, Ramkrishna Care Hospital, Raipur, Chhattisgarh, India

[2,5]Department of Critical Care, Ramkrishna Care Hospital, Raipur, Chhattisgarh, India

[3]Department of Neurosurgery, Ramkrishna Care Hospital, Raipur, Chhattisgarh, India

Corresponding Author: Prawash Kumar Chowdhary, Department of Nephrology, Ramkrishna Care Hospital, Raipur, Chhattisgarh, India, Phone: +91 7389399937, e-mail: prawashchowdhary@yahoo.co.in

How to cite this article: Chowdhary PK, Agrawal RK, Kumar S, Kale SA, Kumar V. Rare and Unusual Presentation as Immune Thrombocytopenic Purpura in Scrub Typhus Complicated by Meningitis and Acute Kidney Injury. Indian J Crit Care Med 2022;26(6):748–751.

Source of support: Nil

Conflict of interest: None

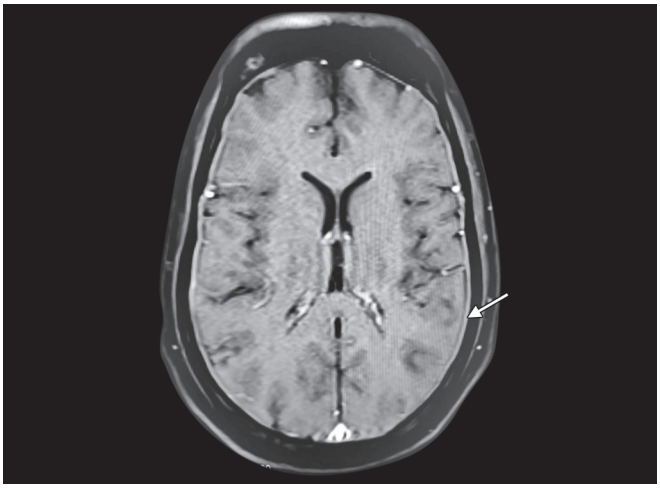

Fig. 1: T1 contrast images showing enhancement of leptomeninges along the bilateral temporoparietal region

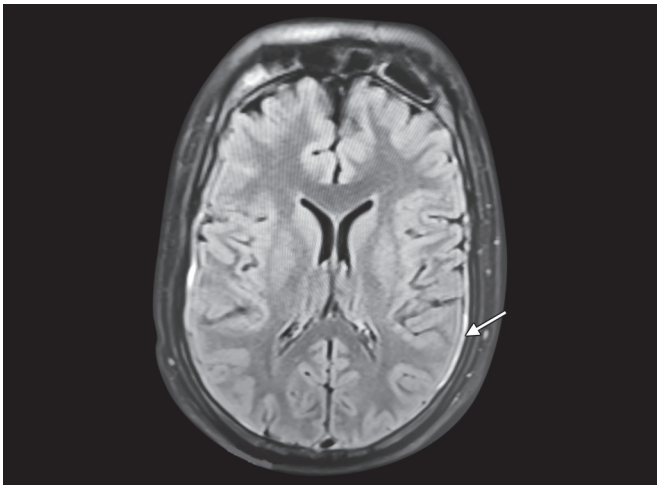

Fig. 2: The FLAIR image shows diffuse thickening of leptomeninges

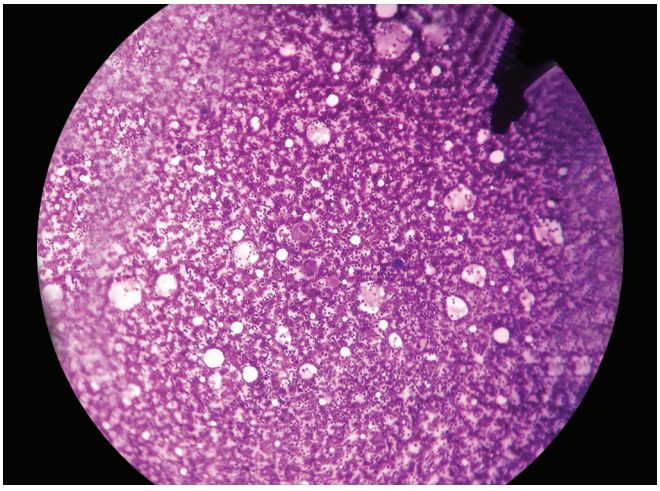

Fig. 3: Microscopic bone marrow examination showing megakaryocytic hyperplasia

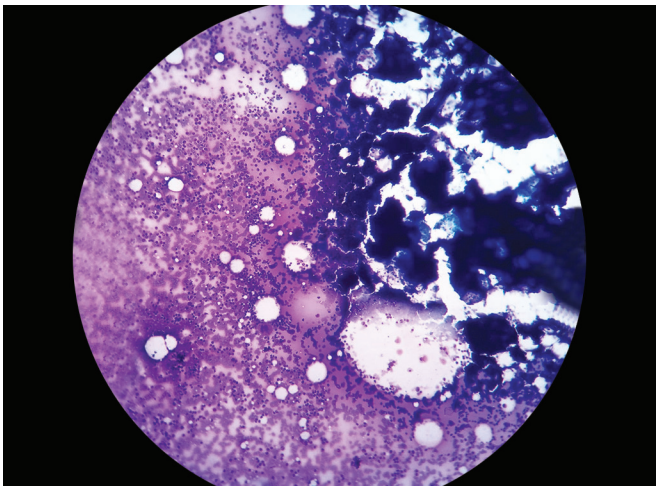

Fig. 4: Microscopic bone marrow examination showing megakaryocytic hyperplasia

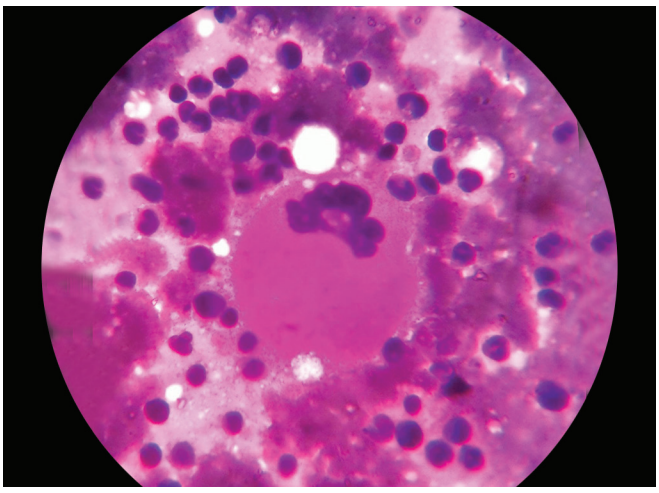

Fig. 5: Microscopic bone marrow examination showing megakaryocytic hyperplasia

of single-donor platelet transfusion increased platelet count from 9,000/cmm^3 to 12,000/mm^3. Immune thrombocytopenic purpura was suspected. After a short course of steroids, there was a significant improvement in the platelet count to 50,000/mm^3. The CSF analysis *via* lumbar puncture showed mild lymphocytic pleocytosis (12 cells) with raised protein (62 mg/dL) and normal glucose. Rifampicin, 600 mg per day, was started to be administered. With this management, his consciousness level and blood parameters, including renal and liver function tests and platelet counts, improved, and discharged in 16 days (Table 1) shows laboratory investigation of the patient.

Discussion

Scrub typhus infections are known to cause an acute febrile illness in tropical regions.[7] Thrombocytopenia is a common manifestation of rickettsial disease. The pathogenesis of thrombocytopenia in rickettsial disease is poorly understood. Thrombocytopenia may be secondary to consumption due to widespread endothelial

Table 1: Laboratory investigation of the patient

Urine	
Albumin	+
Red blood cells	1–2/HPF
Pus cell	2–3/HPF
24 hour; urine protein	268 mg/dL
Hematology	
Hemoglobin (Hb)	12.4 mg/dL
Total leukocytes count (TLC)	21,000/cmm
Differential leukocytes count (DLC)	N82 L16 E2
Erythrocyte sedimentation rate (ESR)	68 mm/hour
Platelet count	9,000/cmm
Peripheral blood smear	Reduced platelet count with no schistocytes
Peripheral smear for malarial parasite	Negative
Biochemical	
Blood urea	96 mg/dL
Serum creatinine	3.08 mg/dL
Serum calcium	8.82 mg/dL
Serum sodium	138 meq/L
Serum potassium	4.8 meq/L
Serum phosphorus	5.1 mg/dL
Serum bilirubin total	3.54 mg/dL
Direct	2.48 mg/dL
Indirect	1.06 mg/dL
Serum alanine transaminase (ALT)	124.6 IU/L
Serum aspartate transaminase (AST)	156.7 IU/L
Total protein	5.5 gm/dL
Serum albumin	2.3 gm/dL
Serum alkaline phosphatase	245.3 U/L
Creatinine phosphokinase (CPK)	43.6 U/L
Lactate dehydrogenase (LDH)	592 IU/L
APTT	Normal
PT with INR	Normal
HIV	Negative
HBsAg	Negative
HCV	Negative
Dengue serology (IgG, IgM, NS1)	Negative
Leptospiral serology (IgM)	Negative
Radiology	
Chest X-ray PA view	Normal
Ultrasonography of abdomen	Liver and spleen not enlarged, No ascites
2D Echocardiography	Normal
Immunology	
Anti-nuclear antibody	Negative
Anti-double-stranded DNA antibody	Negative

damage, disseminated intravascular coagulation, hypersplenism, decreased marrow production, or immune-mediated platelet destruction. Anti-platelet antibodies had been detected in thrombocytopenic patients with the rickettsial disease.[8] Our patient had persistent thrombocytopenia despite single donor platelet transfusion, suggestive of peripheral destruction by preformed antibodies with a clinical diagnosis of immune thrombocytopenic purpura. The platelet count could only improve with steroid administration.

Secondary involvement of the central nervous system is a known complication of scrub typhus, ranging from aseptic meningitis to frank meningoencephalitis.[9] Other neurological complications include seizures, delirium, and hearing loss. Pai et al. identified *O. tsutsugamushi* DNA using nested polymerase chain reaction (PCR) in the CSF in 6 of 25 patients with scrub typhus.[10] As in this case, a mild pleocytosis with lymphocyte dominance and protein levels >45 mg/dL in CSF had been reported in the literature in 48% of cases. Finding of eschar, serological confirmation, and improvement with Doxycycline strongly suggested scrub typhus meningitis.

A careful head-to-toe examination in search of eschar in appropriate cases with early treatment with Doxycycline holds the key to success. Tetracycline 500 mg four times a day (QID) or Doxycycline 200 mg once a day for 7 days is the treatment of choice. Chloramphenicol 500 mg four times a day is an alternative. In Doxycycline-susceptible or -resistant cases, Azithromycin is more efficacious.[11] The present case also has initial deterioration for which Azithromycin was added. Bacteriostatic action or resistances are possible explanations.[11] Doxycycline has a low blood–brain barrier penetrability of 15–30%.

In contrast, in the study, Strickman D et al. demonstrated mean Rifampicin concentration in brain tissue 0.29 µg/mL, and in CSF 0.73 µg/mL, which is higher than minimum inhibitory concentration for *O. tsutsugamushi* 0.0625–0.5 µg/mL.[11] With these results, one should consider the addition of Rifampicin in case of CNS involvement. The cases in our study also showed improvement after the addition of Rifampicin.

The renal involvement in scrub typhus is mostly believed to be a part of multiorgan dysfunction syndrome.[12] The underlying reasons can be categorized as pre-renal or renal. Pre-renal causes lead to impaired renal perfusion secondary to hypovolemia, increased vascular permeability, or rhabdomyolysis. Renal cause includes vasculitis, acute interstitial nephritis, thrombotic microangiopathy secondary to DIC, and acute tubular necrosis due to direct microbial invasion of the renal tubules.[12] Our patient does not show any urinary abnormalities, as seen in 50–80% of the other reports in the literature.[12] Improvement in renal function with conservative management in present cases suggested pre-renal cause of acute kidney injury.

Conclusion

Patients from tropical areas with suggested history should have a high index of suspicion for scrub typhus. Meticulous history, detailed physical examination, and early treatment with Doxycycline are the key to success. Complications with scrub typhus are life-threatening. A physician should be aware of the possible development of meningitis or meningoencephalitis during therapy. Although thrombocytopenia is common in scrub typhus, failure of platelet count to normalize even after the platelet transfusion, and reversal of other components of multiorgan dysfunction, should prompt the clinician to consider the possibilities of immune etiology.

Orcid

Prawash Kumar Chowdhary https://orcid.org/0000-0002-3722-5372
Rakesh Kumar Agrawal https://orcid.org/0000-0002-0711-3150
Sanjeev Kumar https://orcid.org/0000-0003-3071-3063
Sanjeev Anant Kale https://orcid.org/0000-0001-8598-7649
Vishal Kumar https://orcid.org/0000-0002-0938-0623

References

1. Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a new genus, Orientia gen. nov., as *Orientia tsutsugamushi* comb. nov. Int J Syst Bacteriol 1995;45(3):589–591. DOI: 10.1099/00207713-45-3-589.
2. Mahajan SK, Rolain JM, Kashyap R, Bakshi D, Sharma V, Prasher BS, et al. Scrub typhus in Himalayas. Emerg Infect Dis 2006;12(10): 1590–1592. DOI: 10.3201/eid1210.051697.
3. Blewitt B. Fevers of the typhus group in the Bhim Tal area, Kumaun Hills, UP, India. BMJ Military Health 1938;70:379–387. DOI: 10.1136/jramc-70-06-03.
4. Sayen JJ, Pond HS, Forrester JS, Wood FC. Scrub typhus in Assam and Burma; a clinical study of 616 cases. Medicine (Baltimore) 1946;25:155–214. DOI: 10.1097/00005792-194605000-00003.
5. Varghese GM, Abraham OC, Mathai D, Thomas K, Aaron R, Kavitha ML, et al. Scrub typhus among hospitalised patients with febrile illness in South India: magnitude and clinical predictors. J Infect 2006;52(1): 56–60. DOI: 10.1016/j.jinf.2005.02.001.
6. Kawamura A, Jr. Tsutsugamushi disease: an overview, In: A Kawamura, Jr., H. Tanaka, and A. Tamura (ed.), Tsutsugamushi disease. University of Tokyo Press: Tokyo, Japan, 1995, p. 1–34.
7. Abhilash KP, Jeevan JA, Mitra S, Paul N, Murugan TP, Rangaraj A, et al. Acute undifferentiated febrile illness in patients presenting to a tertiary care hospital in South India: clinical spectrum and outcome. J Glob Infect Dis 2016;8(4):147–154. DOI: 10.4103/0974-777X.192966.
8. Kim HA, Lee JY, Hyun M, Ryu SY. A case of immune thrombocytopenic purpura associated with scrub typhus. Korean J Med 2014;86(3): 362–366. DOI: 10.3904/kjm.2014.86.3.362.
9. Vallejo–Maroto I, García–Morillo S, Wittel MB, Stiefela P, Mirandaa M, Pamiesa E, et al. Aseptic meningitis as a delayed neurologic complication of murine typhus. Clin Microbiol Infect 2002;8(12): 826–827. DOI: 10.1046/j.1469-0691.2002.00502.x.
10. Pai H, Sohn S, Seong Y, Kee S, Chang WH, Choe KW. Central nervous system involvement in patients with scrub typhus. Clin Infect Dis 1997;24(3):436–440. DOI: 10.1093/clinids/24.3.436.
11. Strickman D, Sheer T, Salata K, Hershey J, Dasch G, Kelly D, et al. *In vitro* effectiveness of Azithromycin against doxycycline-resistant and -susceptible strains of *Rickettsia tsutsugamushi*, etiologic agent of scrub typhus. Antimicrob Agents Chemother 1995;39(11):2406–2410. DOI: 10.1128/aac.39.11.2406.
12. Sedhain A, Bhattarai GR. Renal manifestation in scrub typhus during a major outbreak in Central Nepal. Indian J Nephrol 2017;27(6):440–445. DOI: 10.4103/ijn.IJN_133_17.