

# Scrub typhus meningitis in a renal transplant recipient

J. Dhanapriya, T. Dineshkumar, R. Sakthirajan, S. Murugan, V. Jayaprakash, T. Balasubramaniyan, N. Gopalakrishnan

Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India

## ABSTRACT

Scrub typhus is a rickettsial infection commonly seen in Asia. The clinical presentation ranges from nonspecific febrile illness to potentially fatal multiorgan involvement such as liver, kidney, or lung. Central nervous system involvement is uncommon. We report a 45-year-old female renal transplant recipient who presented with fever, headache, meningeal signs, graft dysfunction, and eschar. IgM antibodies against *Orientia tsutsugamushi* were positive by enzyme-linked immunosorbent assay. Despite oral doxycycline therapy for 5 days, she did not improve but responded well to intravenous azithromycin. To the best of our knowledge, scrub typhus as a cause of meningitis in a renal transplant recipient has not been reported so far.

**Key words:** Doxycycline, eschar, meningitis, scrub typhus

## Introduction

Scrub typhus is caused by *Orientia tsutsugamushi* of Rickettsiaceae family, an obligate intracellular bacterium. It is transmitted by trombiculid mite bite while field rodents act as reservoirs.<sup>[1]</sup> The infection usually presents as acute febrile illness accompanied by headache, myalgia, vomiting, diarrhea, or cough on 3–4 days and rash/lymphadenopathy at the end of the 1<sup>st</sup> week after bite. During the 2<sup>nd</sup> week of illness, serious complications<sup>[2]</sup> such as pneumonitis, myocarditis, acute kidney injury (AKI), acute respiratory distress syndrome, and multiorgan dysfunction syndrome can occur. Central nervous system (CNS) manifestations of scrub typhus range from aseptic meningitis to frank meningoencephalitis.<sup>[3]</sup> We report here a renal transplant recipient with scrub typhus meningitis who improved after intravenous (IV) azithromycin.

### Address for correspondence:

Dr. J. Dhanapriya,  
Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 600 003, Tamil Nadu, India.  
E-mail: priyamdhana@gmail.com

### Access this article online

#### Quick Response Code:



#### Website:

www.indianjinephrol.org

#### DOI:

10.4103/0971-4065.181883

## Case Report

A 45-year-old woman, renal transplant recipient, presented to us with fever with chills, myalgia, severe headache, and persistent vomiting of 6 days duration. She had undergone deceased donor renal transplant 4 years ago, and did not have any rejection or major infections. She was on triple immunosuppression (tacrolimus - 3 mg/day, mycophenolate mofetil - 1500 mg/day, and prednisolone - 7.5 mg/day) and was maintaining normal graft function. There was no pallor, icterus, lymphadenopathy, rash, or edema. Physical examination revealed pulse rate of 102/min, respiratory rate of 16/min, temperature of 103°F, blood pressure of 120/80 mm Hg, and a circumscribed eschar on the back just below left scapula [Figure 1]. Examination of cardiovascular, respiratory system, and abdomen was normal. Neurological examination revealed neck stiffness, mild irritability with normal mentation, and optic fundus. She was started on oral doxycycline of 100 mg twice daily after clinical diagnosis of scrub typhus meningitis was made. Laboratory investigations revealed urine analysis: Trace proteinuria; total blood count: 6500 cells/mm<sup>3</sup>

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Dhanapriya J, Dineshkumar T, Sakthirajan R, Murugan S, Jayaprakash V, Balasubramaniyan T, *et al.* Scrub typhus meningitis in a renal transplant recipient. Indian J Nephrol 2017;27:151-3.



Figure 1: Clinical photography showing eschar on the back

with a polymorphonuclear predominance; hemoglobin: 11 g/dl, platelet count 100,000 cells/mm<sup>3</sup>; normal peripheral smear; blood urea 60 mg/dl; serum creatinine 1.6 mg/dl; bilirubin 0.8 mg/dl; alanine aminotransferase (ALT) 53 IU/L; aspartate aminotransferase 48 IU/L; alkaline phosphatase 86 IU/L; total protein 6.8 g/dl; and albumin 3.8 g/dl. IgM antibodies against *O. tsutsugamushi* by enzyme-linked immunosorbent assay (ELISA) were positive. Blood and urine cultures were negative. Quantitative buffy coat for malaria, microscopic agglutination tests, and IgM and IgG antibodies for leptospirosis and dengue were negative. Blood polymerase chain reaction (PCR) for cytomegalovirus was negative. Chest X-ray and electrocardiogram were normal. Abdominal ultrasound showed no organomegaly and normal allograft kidney. Computerized tomography of the brain was normal. Cerebrospinal fluid (CSF) analysis showed mild pleocytosis (6–7 cells) mainly lymphocytes, high protein (203 mg/dl), normal sugar (77 mg/dl), normal adenosine deaminase (6 U/L), and negative for tuberculosis and herpes simplex virus by PCR. The patient had persistent fever and headache even after 5 days of oral doxycycline therapy. She was started on IV azithromycin 500 mg/day. She became afebrile within 24 h, her general condition improved dramatically and discharged with normal creatinine. She received totally 1 week of IV azithromycin followed by oral dose for 1 week.

## Discussion

Scrub typhus infection usually occurs during the rainy months of June to November. In recent years, there is increasing occurrence of scrub typhus in India, especially in southern parts.<sup>[4]</sup> The name “typhus” is derived from the Greek word, typhos that means stupor. *O. tsutsugamushi* spreads by blood and lymphatics

and induces generalized vasculitis. Clinical findings include such as fever, maculopapular rash, generalized lymphadenopathy, liver dysfunction, pneumonitis, meningitis/meningoencephalitis, AKI, and septic shock.<sup>[5]</sup> Eschar, which is the pathognomonic sign of scrub typhus, is nonitchy and nonpainful ulcer surrounded by red areolae and covered by dark scabs. It is present in 40–50% of patients and is often present in areas such as groin, gluteal folds, breast folds, and external genitals.<sup>[6]</sup>

The diagnosis of scrub typhus is usually made by either a single indirect immunofluorescent antibody (IFA) titer against *O. tsutsugamushi* of 1/400 or a 4-fold or greater rise in IFA titer. IgM ELISA, based on the detection of 56 Da antigen is a dot blot test which has high specificity (~90%) and sensitivity (~90%) when compared to IFA. A standard PCR targeting the 56-kDa outer membrane protein will be useful but not widely available.<sup>[7]</sup>

In a study of 30 children with scrub typhus in Thailand, only one patient had meningitis.<sup>[8]</sup> A case series of scrub typhus from India reported meningitis as a common CNS complication. Other complications include seizures, delirium, and hearing loss. Focal CNS damage, cerebellitis, myelitis, and cerebral hemorrhage were reported rarely.<sup>[9]</sup> Pai *et al.* identified *O. tsutsugamushi* DNA using nested PCR in the CSF in 6/25 patients with scrub typhus. They reported mild pleocytosis with lymphocyte dominance and protein levels >45 mg/dl in the CSF in 48% of patients.<sup>[10]</sup> A study showed association of pneumonitis was with the occurrence of scrub typhus meningitis and meningoencephalitis.

In a study of 20 consecutive patients with acute encephalitis, 30% were due to scrub typhus.<sup>[11]</sup> Eschar was seen in 50% and renal involvement in 100% of patients. Magnetic resonance imaging brain revealed cerebral edema, bright lesions in the putamen, and the thalamus. All patients responded well to oral doxycycline. The overall mortality rate with scrub typhus meningitis was 25%.

Risk factors for scrub typhus infection are living in rural areas, sleeping outdoors, rapid urbanization, aging populations, and recent rainfall. Our patient was from the rural area and sleeping outdoors in rainy season would have been the risk factor. She had fever, headache, and eschar which was typical presentation of scrub typhus but had meningitis and nonresponsiveness to oral doxycycline which was rare. The causes of meningitis after renal transplantation include bacterial (*Listeria monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Escherichia*

*coli*, etc.), viral (cytomegalovirus, herpes simplex), tuberculosis, fungal (*Cryptococcus neoformans*, *Histoplasma capsulatum*), and parasitic (invasive strongyloidiasis).

The CSF findings in scrub typhus resemble those in viral meningoencephalitis, leptospirosis, and tuberculous meningitis.<sup>[12]</sup> We excluded all these causes in our patient. CSF lymphocyte predominance and elevated serum ALT levels may be helpful in differentiating from bacterial meningitis.<sup>[13]</sup> The transmission of tropical infections in transplant recipients occurs through three routes: donor-Derived infections, reactivation or recrudescence of latent infections, or *de novo* transmission after transplantation. The increasing emphasis on tropical infections in transplant recipients recently is due to include increasing travel of transplanted patients to the tropics, increasing numbers of transplantation, and transplant tourism in tropical countries.<sup>[14]</sup> Apart from tuberculosis, infections such as leprosy, malaria, leishmaniasis, dengue, yellow fever, measles, and leptospirosis have been reported in transplant recipients.

Doxycycline 200 mg/day for 7 days is the treatment of choice. Our patient did not respond to oral doxycycline. Possible explanations for the therapeutic failure of doxycycline include bacteriostatic action, lower penetration into CSF (only 15–30%), and resistance to the drug. Intravenous doxycycline or a higher oral dose may be helpful in achieving higher CSF levels. Chloramphenicol 500 mg, qid or rifampicin 900 mg/day for a week can be used patients who do not respond to conventional therapy. Azithromycin (10 mg/kg/day) has been proven to be more effective in both doxycycline-susceptible and resistant scrub typhus.<sup>[15]</sup> Our patient responded well to IV azithromycin.

## Conclusions

Renal transplant recipients are prone to opportunistic infections. Rare causes such as scrub typhus should also be considered in the case of mononuclear meningitis, especially in endemic areas. Thorough clinical examination and high index of suspicion are needed for early diagnosis and favorable outcome.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, et al. Scrub typhus: An unrecognized threat in South India-clinical profile and predictors of mortality. *Trop Doct* 2010;40:129-33.
2. Mahajan SK. Scrub typhus. *J Assoc Physicians India* 2005;53:954-8.
3. Kim DM, Chung JH, Yun NR, Kim SW, Lee JY, Han MA, et al. Scrub typhus meningitis or meningoencephalitis. *Am J Trop Med Hyg* 2013;89:1206-11.
4. Mathai E, Rolain JM, Verghese GM, Abraham OC, Mathai D, Mathai M, et al. Outbreak of scrub typhus in southern India during the cooler months. *Ann N Y Acad Sci* 2003;990:359-64.
5. Mahajan SK, Rolain JM, Kashyap R, Bakshi D, Sharma V, Prasher BS, et al. Scrub typhus in Himalayas. *Emerg Infect Dis* 2006;12:1590-2.
6. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. *J Assoc Physicians India* 2010;58:24-8.
7. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. *BMC Infect Dis* 2010;10:108.
8. Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children. *Pediatr Infect Dis J* 2003;22:341-5.
9. Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T. Scrub typhus meningitis in South India – A retrospective study. *PLoS One* 2013;8:e66595.
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;24:436-40.
11. Kar A, Dhanaraj M, Dedeepiya D, Harikrishna K. Acute encephalitis syndrome following scrub typhus infection. *Indian J Crit Care Med* 2014;18:453-5.
12. Abhilash KP, Gunasekaran K, Mitra S, Patole S, Sathyendra S, Jasmine S, et al. Scrub typhus meningitis: An under-recognized cause of aseptic meningitis in India. *Neurol India* 2015;63:209-14.
13. Varghese GM, Mathew A, Kumar S, Abraham OC, Trowbridge P, Mathai E. Differential diagnosis of scrub typhus meningitis from bacterial meningitis using clinical and laboratory features. *Neurol India* 2013;61:17-20.
14. Franco-Paredes C, Jacob JT, Hidron A, Rodriguez-Morales AJ, Kuhar D, Caliendo AM. Transplantation and tropical infectious diseases. *Int J Infect Dis* 2010;14:e189-96.
15. Mahajan SK, Rolain JM, Kanga A, Raoult D. Scrub typhus involving central nervous system, India, 2004-2006. *Emerg Infect Dis* 2010;16:1641-3.