



# Dengue and scrub typhus co-infection causing septic shock

Prakriti Subedi <sup>1,\*</sup>, Manoj Ghimire <sup>2</sup>, Karun Shrestha <sup>1</sup>, Kalpana Ghimire<sup>3</sup>, Sudeep Adhikari <sup>4</sup> and Bishal Tiwari<sup>5</sup>

<sup>1</sup>General Medicine, Patan Academy of Health Sciences-School of Medicine, Lalitpur, Nepal

<sup>2</sup>General Medicine, Government of Nepal Ministry of Health and Population, Beni Hospital, Kathmandu, Nepal

<sup>3</sup>General Medicine, Government of Nepal Ministry of Health and Population, Illam District Hospital, Kathmandu, Nepal

<sup>4</sup>Internal Medicine, Patan Academy of Health Sciences-School of Medicine, Lalitpur, Nepal

<sup>5</sup>General Medicine, Ministry of Health and Population Department of Health Services, Beni Hospital, Kathmandu, Nepal

\*Correspondence address. General Medicine, Patan Academy of Health Sciences-School of Medicine, Lalitpur, Nepal. Tel: +977-9841148974;

E-mail: drsubediprakriti@gmail.com

## Abstract

A 33-year-old female presented with a history of high-grade fever, cough, dyspnea, joint pain and myalgia. On examination, the patient was febrile with tachycardia, hypotension and decreased oxygen saturation. Chest auscultation revealed bilateral decreased air entry with crepitation supported by bilateral pulmonary infiltrates on chest X-ray. The laboratory investigations showed leukocytosis, thrombocytopenia, transaminitis and renal impairment. The patient was treated with intravenous fluids, ceftriaxone and levofloxacin; however, there was no clinical improvement till 48 h. She was then diagnosed with scrub typhus and dengue co-infection via serologies. Doxycycline was started following which the patient improved in 24 h. Scrub typhus can present with septic shock but does not respond to the usual antibiotics and the addition of doxycycline will result in rapid clinical improvement. Co-infection with other tropical diseases such as dengue is also common, hence it is important to test based on local endemicity.

## INTRODUCTION

Dengue and scrub typhus are common tropical diseases causing nonspecific febrile illness. Dengue is a mosquito-borne self-limiting viral disease of the tropics, and is transmitted by the bite of female *Aedes* mosquito [1]. Though initially reported only in southern plains of Nepal, recently it has expanded its territory to temperate and subtropical climatic areas in hilly regions, causing an epidemic in 2019 with 17,992 cases reported from all seven provinces of the country [2]. Dengue can present from mild illness with fever, headache, myalgia and rash to severe disease manifesting with shock, narrow pulse pressure, pleural effusion, ascites and bleeding [1].

Scrub typhus is another nonspecific febrile disease caused by the organism *Orientia tsutsugamushi* and is spread to people through bites of infected chiggers (larval mites). The organism is inoculated into the skin after the bite and disseminates widely to target organs infecting the host cells, causing host cell injury. It is endemic in countries within the Tsutsugamushi triangle which includes Nepal [3]. Recently it has also extended globally to areas beyond the Tsutsugamushi triangle [4]. It can range from milder disease with fever, headache, myalgia to severe disease with complications such as acute respiratory distress syndrome, acute kidney injury, disseminated intravascular coagulation, meningoenphalitis,

myocarditis, hemophagocytic syndromes or multiorgan dysfunction [3]. Doxycycline, which is the drug of choice, is bacteriostatic to the *O. tsutsugamushi*, and causes rapid defervescence and clinical improvement within 48 h. If not promptly identified and treated, scrub typhus causes complications and increased mortality. Mortality is ~10% if not treated early [3]. After the 2015 earthquake in Nepal, cases of undifferentiated febrile illness not responding to beta-lactam antibiotics were reported with higher mortality (8%), which were later confirmed to be due to scrub typhus. Scrub typhus is on the rise in Nepal after the earthquake. The mortality later decreased to 1.1% in 2017 with early identification and treatment [5].

Both diseases have several clinical and laboratory features in common, including rash, thrombocytopenia and hepatic dysfunction. However, concurrent infection with both pathogens is rare, primarily due to the different vectors involved. We are presenting a case from *Myagdi*, a hilly district of Nepal who presented with fever, pneumonia and septic shock which was later diagnosed as having dengue and scrub typhus co-infection.

## CASE REPORT

A 33-year-old female, farmer by occupation, living in western Nepal presented to the emergency department of Beni Hospital, *Myagdi* during August 2020,

Received: May 25, 2021. Revised: October 17, 2021. Accepted: October 28, 2021

© The Author(s) 2021. Published by Oxford University Press. All rights reserved. For Permissions, please email: journals.permissions@oup.com

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

**Table 1.** Laboratory investigation report

	At admission	Day 1	Day 4	Day 12	Normal range
White Blood Cells x 10 <sup>9</sup> /L	12.1	11.9	10.2	10.1	4–11
Neutrophils%	78	79	77	76	
Lymphocytes%	23	21	18	19	
Platelets x10 <sup>9</sup> /L	43	40	37	90	150–450
Hemoglobin	9.2	9.5	9.3	9.4	12–15.59 (female)
Total bilirubin (mg/dl)	0.8	0.8	0.7	0.9	0.3–1.2
Direct bilirubin(mg/dl)	0.3	0.3	0.3	0.4	<0.3
Aspartate transaminase (units/L)	92	110	40	31	<31
Alanine transaminase (units/L)	48	60	38	29	10–28
Alkaline phosphatase (IU/L)	372	373	372	370	42–98
International Normalized Ratio	2.1	1.8	1.2	1.1	<1.2
Urea(mg/dl)	40	45	20	19	6–24
Creatinine(mg/dl)	1.6	1.6	1.0	0.9	0.6–1.1 (female)

with a 10-day history of high-grade intermittent fever, associated with chills and rigor. She had 3 days of gradually progressive dyspnea with concomitant headache, nonproductive cough and upper abdominal pain. She also had nausea, retro orbital pain, myalgia, multiple joint pain and chest pain aggravated by cough. She had no history of vomiting, neck pain or stiffness, visual difficulties, rashes, burning or painful urination, or any specific travel history. She took cefixime 200 mg twice daily for 3 days from a local pharmacy without improvement.

On examination, the temperature was 39.9°C, blood pressure was 60/40 mmHg and pulse rate was 116 beats per minute. Her oxygen saturation was 82% in room air and respiratory rate was 26 breaths per minute. There was no jaundice, anemia, edema, lymphadenopathy or rashes. Chest auscultation showed bilateral decreased air entry with crepitations over bilateral infra-scapular and infra-axillary regions. The eschar which is typical of scrub typhus was not observed. The cardiovascular, abdominal and neurological examination findings were unremarkable.

Considering pneumonia with sepsis, normal saline bolus was given immediately in the emergency department. Blood and urine samples were collected for routine tests and culture. Intravenous ceftriaxone 1 g twice daily was then started. Her blood pressure rose to 90/60 mm Hg after 2 litres of normal saline. Supplemental oxygen was given and she was admitted to the ward with the above medications continued.

The lab investigations showed leukocytosis, thrombocytopenia, coagulopathy, transaminitis and renal impairment (values of all these parameters are listed in Table 1). Chest X-ray showed bilateral pulmonary infiltrates. There was no clinical improvement at 48 h after starting ceftriaxone. In view of recently increased cases of dengue and scrub typhus in Myagdi district, we sent blood for serology for these diseases. Dengue IgM and scrub typhus IgM both came positive. Serologies for leptospirosis and malaria were negative. Blood culture revealed no growth of any organism. COVID-19 polymerase chain reaction test was negative.

Then, tablet doxycycline 100 mg twice daily was added to the therapy with continued ceftriaxone and normal saline. Following treatment with oral doxycycline, she showed rapid defervescence and clinical improvement in 24 h. Blood and urine culture did not show any growth. Normal saline infusion was stopped on the third day. On the fourth day of admission, she was able to maintain an oxygen saturation of 94% at room air and repeated tests for initial abnormal parameters normalized (Table 1). Ceftriaxone was stopped on the fifth day and she was discharged with doxycycline for a total of 7 days. She was well and most of her laboratory parameters had improved (Table 1) when she came for the follow-up after 1 week.

## DISCUSSION

In this case, the patient presented with respiratory symptoms and signs of multiorgan dysfunction (respiratory dysfunction, renal impairment, transaminitis, coagulopathy and thrombocytopenia) with septic shock. Our local protocol is to start the treatment based on severity, with intravenous ceftriaxone or broad-spectrum antibiotics such as piperacillin, carbapenems or fourth-generation cephalosporin combined with quinolones or aminoglycoside with or without vancomycin for methicillin resistant *Staphylococcus aureus* (MRSA) coverage [6]. However, this empirical treatment does not offer coverage of rickettsia, which is commonly neglected as a differential diagnosis for a nonspecific febrile presentation.

Diagnosis of scrub typhus and dengue co-infection with multiorgan dysfunction was made in the patient, and treated accordingly. The co-infection is rare, and we made the diagnosis relying on serologies for both scrub typhus and dengue which could be questioned for accuracy. Rapid diagnostic kit Dengue Day 1 Test (J. Mitras and Company Pvt. Ltd., India) was used for diagnosing dengue infection. Manufacturer reported sensitivity and specificity for both NS1 antigen and IgM antibody are above 95% for diagnosing the acute dengue infection. Scrub typhus was diagnosed using Scrub Typhus Detect IgM ELISA (InBios, USA), which has sensitivity of 93% and

specificity of 91%. Serological tests, particularly those relying on IgM and targeting Rickettsia, are known to cross-react to other antigens, and use of polymerase chain reaction is commonly advocated as confirmatory test in this setting [7]. However, this is not available in our resource-limited setting in Nepal and clinicians must interpret the available test results with knowledge of these limitations. Also Nepal is endemic for scrub typhus, and has also been experiencing outbreaks of dengue since some years recently. This case occurred during August (monsoon season in Nepal), which is the favorable time for both diseases. Moreover, the patient is a farmer who has higher possibilities of being exposed to the vectors—mites and mosquitoes. So, we relied on these tests and the diagnosis of scrub typhus was also supported by response to doxycycline. We suppose the concomitant acquisition of both diseases is not very unlikely given the epidemiology of these diseases in Nepal.

Scrub typhus cannot reliably be distinguished from other febrile illnesses. The eschar, which is usually considered pathognomonic for scrub typhus, is not common in patients in Nepal [8]. Also the location of eschar may be different in males and females. IgM ELISA is usually adopted to make a diagnosis which is not readily available in all health centers. Sometimes it may be murine typhus (also responsive to doxycycline) but the test for it is not available in Nepal [9].

Considering the diagnostic difficulties and the need for prompt and appropriate treatment, empirical use of doxycycline along with ceftriaxone is encouraged in patients presenting with fever and multisystem involvement in countries like Nepal, especially in the rural health settings. With the use of doxycycline, remarkable clinical improvement with defervescence within 48 h can be used as the therapeutic diagnosis for scrub typhus as such dramatic response cannot be expected in other usual bacterial causes of pneumonia-like pneumococcal pneumonia even with the use of appropriate antibiotics [10].

Our patient also had co-infection with dengue, and thrombocytopenia, shock and transaminitis could have been implicated to severe dengue. However, there was no evidence of plasma leakage like hemoconcentration or effusions [1]. Accordingly, severe dengue disease was ruled out in the patient and treatment was given with the diagnosis of scrub typhus with multisystem involvement, which later resolved rapidly with the initiation of doxycycline.

## CONCLUSIONS

Scrub typhus can present with fever with multi-organ dysfunction causing septic shock, but the disease does not respond to usual sepsis antibiotics protocol. Addition of doxycycline empirically to the initial regimen will result in rapid clinical improvement. Co-infection with other tropical diseases such as dengue is also common,

hence it is important to perform a panel of tests based on local endemicity.

## ACKNOWLEDGEMENTS

We would like to thank the patient and his family members. We would also like to thank Beni hospital staff for the cordial support.

## CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

## FUNDING

None.

## ETHICAL APPROVAL

Not required.

## CONSENT

Written informed consent was obtained from the patient for publication of this case report.

## GUARANTOR

Prakriti Subedi.

## References

1. Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. *N Engl J Med* 2012;**366**:1423–32.
2. Rijal KR, Adhikari B, Ghimire B, Dhungel B, Pyakurel UR, Shah P et al. Epidemiology of dengue virus infections in Nepal, 2006–2019. *Infect Dis Poverty* 2021;**10**:52.
3. Paris DH, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. *Am J Trop Med Hyg* 2013;**89**:301–7.
4. Weitzel T, Martínez-Valdebenito C, Acosta-Jamett G, Jiang J, Richards AL, Abarca K. Scrub typhus in continental Chile, 2016–2018. *Emerg Infect Dis* 2019;**25**:1214–7.
5. Dhimal M, Dumre SP, Sharma GN, Khanal P, Ranabhat K, Shah LP et al. An outbreak investigation of scrub typhus in Nepal: confirmation of local transmission. *BMC Infect Dis* 2021;**21**:193.
6. Khilnani GC, Zirpe K, Hadda V, Mehta Y, Madan K, Kulkarni A et al. Guidelines for antibiotic prescription in intensive care unit. *Indian J Crit Care Med* 2019;**23**:S1–s63.
7. Abdad MY, Abou Abdallah R, Fournier PE, Stenos J, Vasoo S. A concise review of the epidemiology and diagnostics of rickettsioses: rickettsia and Orientia spp. *J Clin Microbiol* 2018;**56**:e01728–17.
8. Basnyat B, Belbase RH, Zimmerman MD, Woods CW, Reller LB, Murdoch DR. Clinical features of scrub typhus. *Clin Infect Dis* 2006;**42**:1505–6.
9. Thompson CN, Blacksell SD, Paris DH, Arjyal A, Karkey A, Dongol S et al. Undifferentiated febrile illness in Kathmandu, Nepal. *Am J Trop Med Hyg* 2015;**92**:875–8.
10. Phimda K, Hoontrakul S, Suttinont C, Chareonwat S, Losuwanaluk K, Chueasuwanchai S et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. *Antimicrob Agents Chemother* 2007;**51**:3259–63.