

Dengue and Scrub Typhus Coinfection: A Diagnostic Dilemma

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Abstract

Due to many overlapping clinical features, scrub typhus infection may be missed in presence of dengue. Concurrent infection with those two pathogens is very rare and creates diagnostic dilemma. We present a case of a 65-year-old male who was admitted with high grade fever and maculopapular rash. Complete hemogram revealed thrombocytopenia with raised hematocrit and positive diagnostic tests for dengue. Patient was treated conservatively with intravenous fluids and antipyretic medications to which the hematocrit improved and the rash disappeared. But fever with thrombocytopenia continued to persist. On further meticulous clinical examination, a small eschar was noted over his abdomen. Doxycycline was started to which the fever subsided and thrombocytopenia improved. Subsequently, scrub serology came positive. This case illustrates the importance of early recognition of coinfection in unremitting febrile illness in tropical countries to prevent their fatal complications.

Keywords: Dengue Fever; Scrub Typhus; Eschar; Thrombocytopenia; Doxycycline.

Introduction

Dengue fever and scrub typhus are two common infections of tropical countries which share many common demographic, clinical and laboratory features. While scrub typhus is a potentially life-threatening arthropod borne infection caused by *Orientia tsutsugamushi*, dengue is a mosquito borne arbovirus infection transmitted by the bite of *Aedes aegypti*.^{1,2} Both the infections are prevalent individually and despite similarities, coinfection is an exceedingly rare entity.³ This may be due to involvement of different vectors, low level of suspicion or a lack of adequate diagnostic facilities. Here we present a case of scrub typhus and dengue coinfection in a 65-year-old gentleman.

Case Report

A 65-year-old gentleman without any comorbidity was admitted to our facility in 2019 with a history of intermittent and high-grade fever associated with bodyache for the last 4 days. It was associated with headache, nausea and vomiting for the same duration. There was no cough, breathlessness, abdominal pain, burning sensation of urine or any bleeding manifestations. He had a history of travel to the hilly areas of Bhutan just 2 weeks prior to the illness.

On examination, patient was fully conscious, oriented and febrile (oral temperature of 101.8 F). His pulse rate was 104 beats/ minute, blood pressure 100/60 mm Hg, respiratory rate 20/minute and peripheral oxygen saturation was

97% on room air. There was maculopapular, blanching rash involving chest, abdomen, back, both upper and lower limbs. There was no lymphadenopathy or organomegaly. Rest of the systemic examinations was unremarkable.

Hematological and biochemical investigations revealed normocytic normochromic anemia, leukocytosis, raised liver enzymes and thrombocytopenia. Thick and thin smear for malaria parasites and malarial antigen test were negative. NS1 antigen by antigen-capture enzyme-linked immunoassay (ELISA) was found to be positive. Ultrasonography of whole abdomen and chest radiography did not reveal any abnormality. Blood and urine for culture showed no growth. A summary of the results of his laboratory tests is shown in **table 1 and table 2**.

Table 1: Summary of the important laboratory tests.

Tests	Results	Normal range
Hemoglobin	10.2	12-16 gm/dl
Total Leukocyte count	15,300	4000-11000 /cumm
Neutrophil	70	40-75%
Lymphocyte	22	20-40%
Prothrombin time(PT)	17.5	11-13.5 s
Activated partial thromboplastin time (APTT)	39.6	30-40 s
Creatinine(cr)	0.8 mg/dl	0.5-1.5 mg/dl
Albumin	2.9 g/dl	3.2-5 g/dl
Total bilirubin	0.9 mg/dl	0.1-1 mg/dl
Alanine transaminase (ALT)	78 IU/L	5-35 IU/L
Aspartate transaminase (AST)	94 IU/L	5-35 IU/L
Alkaline phosphatase (ALP)	333 IU/L	110-310 IU/L
Fasting blood sugar	81 mg/dl	75-110 mg/dl

Table 2: Change of Platelet counts and PCV after admission.

	On Admission	Day 2	Day 3	Day 4	Reference range
Platelet count/microlitre	44,000	72,000	66,000	78,000	1.5-4.5 lakhs/microlitre
Packed cell volume(PCV)	53%	51%	48%	43%	42-52%

Patient was treated conservatively with intravenous fluids, antiemetic and antipyretic medications. Hydration was adequately maintained. Over the next 4 days of hospitalization, although the hematocrit improved and the blanching rash disappeared, the high grade fever with thrombocytopenia continued to persist.

As the patient continued to deteriorate clinically, we decided to perform a series of tests to exclude any coinfection and to look for other foci of infection. On further meticulous clinical examination, a small necrotic eschar was noted over his abdomen. (**Figure 1**) Serology for scrub typhus, leptospira and chikungunya were sent and oral tablet doxycycline (100mg) twice daily was started on the basis of strong clinical suspicion. Two days later, blood for scrub IgM report came to be positive (O.D: 2.2188 by ELISA) and doxycycline was continued for 10 days. Leptospira and chikungunya serology were negative. Degue IgM capture ELISA was positive in high titre. Patient became afebrile within 2 days and the platelet count improved. Patient was discharged after 4 days; he had an uneventful recovery and was followed up in our outpatient department. Repeat scrub typhus IgM antibody assay showed a decline of the IgM from the initial levels (O.D: 1.1226 by ELISA).



Figure 1: Clinical picture showing the pathognomonic eschar on the abdomen.

Discussion

The onset of scrub typhus is characterized by fever, cough, headache, myalgia and gastrointestinal symptoms.⁴The characteristic findings include a necrotic eschar along with regional lymphadenopathy, interstitial pneumonia, encephalitis and a maculopapular rash. Studies have shown leukocytosis, transaminitis with or without cholestasis and hepatosplenomegaly in patients with scrub typhus.⁵The spectrum of dengue fever is wide and is characterized by high grade fever, headache, retroorbital pain, transient blanching rash and hemorrhagic complications, leading to rapid deterioration with development of shock syndrome.⁶The generalized confluent erythematous rash with multiple small islets of normal skin often gives rise to a classical cutaneous sign in dengue, which is known as ‘White islands in a sea of red’ sign.⁷ Isolation of dengue virus (DENV) or detection by molecular methods such as reverse-transcription polymerase chain reaction (RT-PCR) is specific for diagnosing infection, but in resource-poor countries like India, NS1 antigen assay along with serology (IgM and/or IgG) has been seen very effective as diagnostic tool.⁸ Recently, rapid diagnostic tests (RDT) have been developed for the detection of dengue NS1 antigen and IgM/IgG antibodies, which are based mainly on immunochromatographic method. Results of such tests can be obtained within 30 minutes. Although RDT was previously considered as a relatively inaccurate tool in diagnosis of dengue; but a recently

published study has concluded that RDT had a high sensitivity and specificity in diagnosis, although the clinicians should correlate the positive or negative results with the clinical signs and symptoms.⁹

According to Watt G et al, median duration of fever at initial presentation was more in scrub typhus (9 days) than in dengue (4 days), lymphadenopathy was more commonly found in scrub typhus (40%) than in dengue (22%) and indoor occupation was more commonly associated with dengue (51%) than scrub typhus (15%).¹⁰ Bleeding manifestations such as bleeding from the gums were more commonly seen in dengue fever than scrub typhus. The macular blanching rash of dengue is subtle as compared to scrub typhus. A low leukocyte count (<5000/mm³) and a low platelet count (<140,000/mm³) are more commonly associated with dengue infections. Low platelet count is also a feature of scrub typhus but usually associated with leukocytosis. Aspartate aminotransferase (AST) > Alanine aminotransferase (ALT) is found in both the diseases but in scrub typhus, elevated levels of alkaline phosphatase is also seen.¹¹ The presence of thrombocytopenia with blanching rash in our patient favored dengue fever but absence of hemorrhagic complications despite thrombocytopenia, elevated total leukocyte count, AST>ALT and mildly elevated alkaline phosphatase favored scrub typhus. Severe thrombocytopenia, high AST and ALT with low albumin have been reported in coinfections.¹²

Though scrub typhus and dengue fever share many common characteristics causing diagnostic dilemma, concurrent infection with both of them are very rare. A case of dengue and scrub typhus coinfection presenting as acute febrile illness in a 50-year-old female from southern belt of Nepal was reported by Sapkota S et al.³ Another case of coinfection was reported by Garg A et al. from Uttar Pradesh, India in a 45-year-old male who presented with fever, hepatic and pancreatic dysfunction and pneumonia. The patient responded well to oral doxycycline.¹³ Raina S et al. evaluated dual infection as etiology of febrile illness in the sub-Himalayan region of north India, where they found dengue and scrub typhus coinfection as an important cause in a few patients.¹⁴ Table 3 summarizes the previous published case reports/case series of dengue and scrub typhus coinfection.^{3,12-15}

Table 3: Comparison of clinical characteristics of previous case reports/case series of dengue and scrub typhus coinfection.

Case report (year)	Country/Region	Age, sex	Travel/Exposure history	Clinical Presentation	Laboratory Parameters	Treatment	Outcome
Sapkota S et al (2017)	Southern belt of Nepal	50, Female	Regular visit to the nearby forest	Fever, headache, bodyache, jaundice, lymphadenopathy, eschar on right deltoid	Leukocytosis, thrombocytopenia, elevated bilirubin and transaminases	Intravenous ceftriaxone and oral doxycycline for 7 days	Discharged on the 7 th day of admission
Subedi P et al (2021)	Western Nepal	33, Female	None	High-grade-fever, cough, dyspnea, arthralgia followed by septic shock. No eschar	Leukocytosis, thrombocytopenia, transaminitis, renal impairment and bilateral pulmonary infiltrates	Oral doxycycline for 7 days	Discharged on the 7 th day of admission
Garg A et al (2018)	Uttar Pradesh, India	45, Male	Travel to sub-Himalayan region of Uttarakhand prior to fever	High-grade fever, pedal edema, facial puffiness and dyspnea. Necrotic eschar on the dorsum of penis.	Initial leukopenia followed by leukocytosis, thrombocytopenia, elevated bilirubin, transaminases, amylase and lipase. Bilateral bronchopneumonia, features of pancreatitis on abdominal imaging.	Intravenous ceftriaxone and oral doxycycline for 7 days	Discharged on the 7 th day of admission

Basheer A et al (2016) Case series	South India	Mean age-42.5; 67% Males	Not mentioned	Fever in all, arthralgia in 3 patients, diffuse blanching rashes and lymphadenopathy in 2 patients. Eschar noted in 2 patients (one in groin and other in axilla)	1 patient had leukocytosis, all others had normal or reduced leukocytes count. Thrombocytopenia, hepatic transaminitis and hypoalbuminemia was seen in almost all.	All the 6 patients received antibiotics- 4 of them were prescribed oral doxycycline, and others azithromycin.	All of them responded to the antibiotic within 48 hours and the temperature touched baseline.
Raina S et al(2018) Case Series	Northern hilly state of Himachal Pradesh, India	Mean age-36.6; 9/10 male	Out of 10 patients, 4 had no history of travel outside Himachal Pradesh	Fever in all; myalgia in 8; cough in 2; dyspnea, oliguria, seizure and bleeding manifestation in 1 each	Out of 10 patients, 8 had thrombocytopenia. The mean ALT and AST was 114 and 161 IU/L respectively.	Not mentioned	All the patients improved at the time of discharge.
Present case (2022)	West Bengal, India	65, Male	Recent history of travel to Bhutan	A high-grade fever, headache, bodyache, vomiting, maculopapular and blanching rash, small necrotic eschar over abdomen	Normocytic normochromic anemia, leukocytosis, raised liver enzymes and thrombocytopenia. No pulmonary infiltrate	Oral doxycycline for 7 days	Resolution of fever within 2 days and discharged after 4 days of initiation of doxycycline.

ALT: alanine transaminase; AST: aspartate aminotransferase

Therefore, high degree of suspicion for coinfection should be made in cases of febrile illness in tropical countries, particularly in monsoon or post-monsoon season to prevent fatal consequences.

Conclusion

Due to overlapping clinical features and similar laboratory features, early diagnosis and treatment of coinfection pose a challenge to the physician. They should be thought of early because delay in diagnosis can lead to longer duration of hospital stay, increased chances of end organ dysfunction and mortality. High index of suspicion should be made in patients from endemic areas presenting with febrile illness with multisystem involvement with deranged laboratory features and not responding to treatment. Meticulous knowledge of the physician regarding endemicity is the key in diagnosing such conditions.

References

1. Rapsang AG, Bhattacharyya P. Scrub typhus. Indian J Anaesth. 2013 Mar;57(2):127-34. doi: 10.4103/0019-5049.111835. PMID: 23825810
2. Khetarpal N, Khanna I. Dengue Fever: Causes, Complications, and Vaccine Strategies. J Immunol Res. 2016;2016:6803098. doi: 10.1155/2016/6803098. Epub 2016 Jul 20. PMID: 27525287; PMCID: PMC4971387.
3. Sapkota S, Bhandari S, Sapkota S, Hamal R. Dengue and Scrub Typhus Coinfection in a Patient Presenting with Febrile Illness. Case Rep Infect Dis. 2017;2017:6214083. doi: 10.1155/2017/6214083. PMID: 28386493
4. Mahajan SK. Scrub typhus. J Assoc Physicians India 2005;53:954-8.
5. Hu ML, Liu JW, Wu KL, Lu SN, Chiou SS, Kuo CH, et al. Short report: Abnormal liver function in scrub typhus. Am J Trop Med Hyg. 2005;73(4):667-668.

6. Kamath SR, Ranjit S. Clinical features, complications and atypical manifestations of children with severe forms of dengue hemorrhagic fever in South India. *Indian J Pediatr.* 2006 Oct;73(10):889-95. doi: 10.1007/BF02859281. PMID: 17090900; PMCID: PMC7101810.
7. Amrani A, Sil A, Das A. Cutaneous signs in infectious diseases. *Indian J Dermatol Venereol Leprol.* 2021 Aug 5:1-7. doi: 10.25259/IJDVL_727_20. PMID: 34379950
8. Muller DA, Depelseñaire AC, Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection. *J Infect Dis.* 2017 Mar 1;215(suppl_2):S89-S95. doi: 10.1093/infdis/jiw649. PMID: 28403441.
9. Yow KS, Aik J, Tan EY, Ng LC, Lai YL. Rapid diagnostic tests for the detection of recent dengue infections: An evaluation of six kits on clinical specimens. *PLoS One.* 2021 Apr 1;16(4):e0249602. doi: 10.1371/journal.pone.0249602. PMID: 33793682; PMCID
10. Watt G, Jongsakul K, Chouriyagune C, Paris R. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. *Am J Trop Med Hyg.* 2003;68(5):536-8.
11. Thap LC, Supananond W, Treeprasertsuk S, Kitvatanachai S, Chinprasatsak S, Phonrat B. Septic shock secondary to scrub typhus: characteristics and complications. *Southeast Asian J Trop Med Pub Health.* 2002;33(4):780-6.
12. Basheer A, Iqbal N, Mookkappan S, Anitha P, Nair S, Kanungo R, *et al.* Clinical and Laboratory Characteristics of Dengue-Orientia tsutsugamushi co-Infection from a Tertiary Care Center in South India. *Mediterr J Hematol Infect Dis.* 2016 Jun 16;8(1):e2016028. doi: 10.4084/MJHID.2016.028. PMID: 27413521
13. Garg A, Jain A, Kashyap R. Travel-acquired Scrub Typhus Infection Masked by Dengue Fever in a Patient from Nonendemic Area. *J Glob Infect Dis.* 2018 Apr-Jun;10(2):114-115. doi: 10.4103/jgid.jgid_68_17. PMID: 29910575
14. Raina S, Raina RK, Agarwala N, Raina SK, Sharma R. Coinfections as an aetiology of acute undifferentiated febrile illness among adult patients in the sub-Himalayan region of north India. *J Vector Borne Dis.* 2018 Apr-Jun;55(2):130-136. doi: 10.4103/0972-9062.242560. PMID: 30280711
15. Subedi P, Ghimire M, Shrestha K, Ghimire K, Adhikari S, Tiwari B. Dengue and scrub typhus co-infection causing septic shock. *Oxf Med Case Reports.* 2021 Dec 11;2021(11):omab115. doi: 10.1093/omcr/omab115. PMID: 34909204