



Scrub Typhus in Intensive Care Unit in Kathmandu – A case series from a tertiary center.

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ABSTRACT:

Scrub typhus is a rickettsial zoonosis caused by *Orientia tsutsugamushi* which can cause focal or disseminated vasculitis & perivasculitis in various body systems. It is endemic in many parts of Nepal & has been neglected & under-detected. We clinically assessed six patients from an intensive care unit in a tertiary hospital in Nepal that tested positive for scrub typhus using IgM ELISA & analyzed their profiles.

Out of six patients, three were male & three were female with a mean age of 44.6 years. All six patients had chief complaints of fever & myalgia. Four patients presented with eschar. Three patients presented with septic shock while one presented with septicemia and meningoenzephalitis. Only one patient had elevated white cell counts. Four out of six patients had transaminitis. Thrombocytopenia was present in two patients. Hypoalbuminemia was present in three patients. All cases tested negative for dengue, malaria, brucella, *Leptospira*, leishmania, salmonella & tuberculosis.

This study points out the need for raising the index of suspicion & early screening of scrub typhus in patients with fever & laboratory findings of liver dysfunction or thrombocytopenia even with normal white cell counts.

Keywords: Scrub typhus, Zoonosis, Transaminitis, Thrombocytopenia



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INTRODUCTION:

Scrub typhus is a zoonotic infection caused by the rickettsial bacteria *Orientia tsutsugamushi* & is transmitted through the bites of larvae of certain trombiculid mites¹. It is most prevalent in a triangular region bounded by Japan, Pakistan, and Australia, known as the "Tsutsugamushi triangle"^{1,2}. It is endemic in many parts of Nepal accounting for 101 cases from 16 districts of Nepal with an 8% case fatality rate in 2015. While in 2016 there were more than 800 reported cases and 14 deaths from the disease⁵. After the initial incubation period of 6-21 days, the disease presents with fever, headache, rash, lymphadenopathy, myalgia, cough, and gastrointestinal symptoms¹. The objective of our study is to demonstrate the clinical features & associated laboratory findings of scrub typhus in an ICU of a tertiary hospital in Nepal.

CASE REPORTS:

Kathmandu is the capital city of Nepal with a population of 1 million. It has the major tertiary centers and is the main referral center from all over the country. After obtaining informed consent, we collected the clinical profiles of six patients identified as Scrub Typhus positive by enzyme-linked immunosorbent assay at National Public Health Laboratory,

Kathmandu and admitted in an ICU of Kathmandu Medical College Teaching Hospital (patients 1-6) from September 1, 2016 to October 1, 2017. This included history, clinical examination & laboratory investigation findings including complete blood count, liver function tests, renal function tests & screening for other possible infections like dengue, malaria, brucella, *Leptospira*, leishmania, salmonella & tuberculosis.

Patient 1:

A 27-year-old male from Sarlahi, Nepal, presented with twelve days history of fever and dry cough. His fever did not have any diurnal variation. There was no change in the character of cough since the onset. He did have some dyspnea on exertion, but his overall mobility had been limited by lethargy and myalgia. He did not have any other medical comorbidities. On presentation, his blood pressure was 80/50 mmHg, tachycardia with pulse of 110 beats per minute. On examination, he had regional axillary lymphadenopathy and inspiratory crackles were present in right lower lung base.

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Chest X-ray showed right lower zone infiltrate with blunting of bilateral costophrenic angles suggestive of bilateral minimal pleural effusion. Blood work showed Hemoglobin (Hb) of 14.1 gm/dl, leukocyte counts of 10,300/mm³, with a neutrophil count of 64% and Lymphocyte counts of 33%. Platelet counts were reduced at 54000/mm³. His renal function was normal with urea of 32 mg/dl and creatinine of 0.8 mg/dl. Electrolytes were normal with sodium of 143 mEq/L and potassium of 4.2 mEq/L. Total bilirubin was 1.6 mg/dl with a direct bilirubin of 0.9 mg/dl. Liver enzymes were slightly elevated with SGOT of 185 IU/L, SGPT 105 IU/L, and ALP of 397 IU/L. He was transferred to the Intensive Care Unit (ICU) and was transferred to general floors after one day in ICU. He was successfully treated with Doxycycline and discharged after 8 days of hospital stay.

Patient 2:

A 67-year-old female from Kanchanpur, Nepal, presented with fever for eight days and altered mental status for four days. She was treated for hypertension for the past four years. On review of system, she did not have any cough or shortness of breath. Vitals were significant with blood pressure of 80/60 mmHg, tachycardic with pulse of 120 beats per minute, regional lymphadenopathy was present on exam. Glasgow coma scale (GCS) was 12/15 (Eye opening 4 Verbal 2 Motor 6) with presence of neck rigidity. Cerebrospinal fluid analysis showed total count of 30 per mL, with differential of 85% lymphocytes, and 15% of neutrophils, glucose of 70 mg/dl, protein of 1800 mg/l, Adenosine Deaminase (ADA) of 18 U/L. Gram stain, Acid-Fast Bacillus (AFB) were negative. Further lab works showed Hb of 9 gm/dl, total count of 18100/mm³, platelets of 170,000/mm³. She had AKI with Urea of 134 mg/dl and creatinine of 1.9 mg/dl. Total bilirubin was 4.9 mg/dl, direct bilirubin was 0.7 mg/dl. Slightly elevated SGPT and SGOT at 78 IU/L and 73 IU/L respectively and ALP of 717 IU/L. Her amylase was 633 U/L and lipase was 993 U/L, with Lactate Dehydrogenase (LDH) of 394 U/L. Dengue IgM and IgG were negative, Malarial parasite antigen was negative, thick and thin smear negative, Brucella antibody test was negative, Leptospira IgG and IgM were negative, Kalazar antigen was negative. She was treated in ICU for Two day, with improvement of symptoms with Doxycycline. Total hospital course was eight days.

Patient 3:

A 52-year-old female from Jiri, Nepal presented with chief complaint of on and off fever since nearly 20 days, cough and shortness of breath in the last 20 days. On examination, she had bilateral wheeze on lung exam. Her counts were normal, renal function were normal. Liver enzymes were mildly elevated with AST 201 IU/L, ALT of 1046 IU/L. Scrub typhus ELISA was positive. Brucella and Leptospira were negative. She was successfully treated with Azithromycin and remained in ICU for four days. Total days of illness from the onset was 35 days.

Patient 4:

A 55-year-old male from Kavre, Nepal presented with fever for ten days. Three days after initial symptoms of fever, she started to have cough which progressively got worse and three days prior to presentation she had shortness of breath. On examination, her blood pressure was 80/60 mmHg, tachycardia with pulse of 120 beats per minute. She had inspiratory crepitus on the lower lung regions. Labs showed Hb of 12.3 g/dl, Total count 10,500/mm³, differential count with neutrophils of 82%, lymphocytes of 15%. Liver function showed AST of 114 IU/L and ALT of 115 IU/L, with ALP of 570 IU/L. Her LDH was 361 U/L. Chest Xray showed right sided pleural effusion. Fluid studies after thoracentesis showed leucocyte count of 100/mm³, lymphocyte of 95%, glucose of 139 mg/dl, LDH of 156 U/L. His Scrub typhus ELISA was positive and was successfully treated with Doxycycline. He was discharged after total ICU stay of four days.

Patient 5:

35-year-old male from Dhangadhi, Nepal presented with fever for seven days, without any cough, nor shortness of breath. His mentation was intact on presentation. Vitals with blood pressure of 110/70 mm/Hg, non-tachycardic with pulse less than 100 beats per minute. He had regional lymphadenopathy. Examination, including skin, cranial nerves, heart and lungs were within normal limits and non-contributory. Labs showed Hb of 14.3 g/dl, total counts of 8400/mm³, platelets of 120,000/mm³. Normal renal functions with urea of 30 mg/dl, creatinine of 1.2 mg/dl. Hepatic panel was normal as well with total bilirubin of 1 mg/dl, direct of 0.3 mg/dl, SGOT 35 IU/L, SGPT 38 IU/L, and ALP 110 IU/L. Scrub Typhus ELISA was positive. Rest of the tests were negative for Dengue, malarial parasite antigen, Brucella, and Leptospira. He was successfully treated with Doxycycline with total ICU stay of three days.

Patient 6:

32-year-old female from Bharatpur, Nepal presented with seven days of fever. She denied any chest pain, shortness of breath or cough. On presentation she was in no distress with normal vitals, blood pressure of 110/70 mmHg, pulse of 90 beats per minute and saturating well in room air. Her mentation was normal with negative neck rigidity. Her lung examination was normal. Labs showed Hb of 12.5 gm/dl, total count of 7300/mm³, platelets of 160,000/mm³. Renal function was normal with Urea of 28 mg/dl, creatinine of 0.9 mg/dl. Total bilirubin of 1.1 mg/dl, direct bilirubin of 0.2 mg/dl, SGOT of 40 IU/L, SGPT 38 IU/L, ALP 115 IU/L. Scrub typhus ELISA was positive. She was successfully treated with Azithromycin and discharged after four days of hospital stay.

In summary, among the six patients half were male and half female. Their mean age was 44.6±15.6 years. Figure 1 shows the geographical location of the six confirmed cases. The duration of illness before hospitalization ranged from 8-20 days with an average of 12.5 days. All six cases

presented with chief complains of fever and diffuse myalgia. Cough and shortness of breath were present in four out of six patients (66.7%), while one had altered sensorium and intense generalized headache. Three patients presented with septic shock while one presented with septicemia and meningoencephalitis.

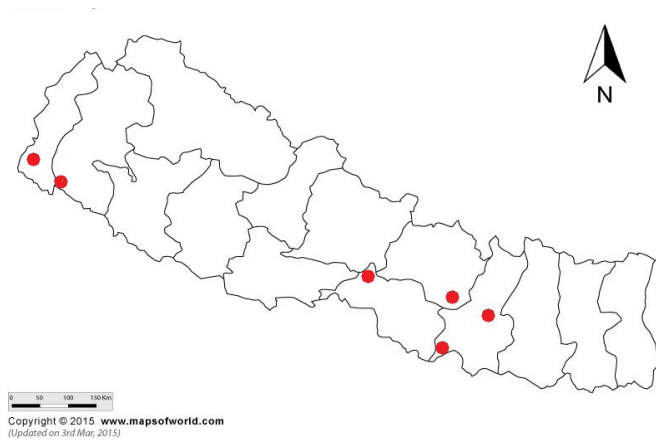


Fig 1 Distribution of laboratory confirmed cases of Scrub Typhus in Nepal, by location (red dots), between 2016 to 2017 confirmed by Rapid ELISA test at National Public Health Laboratory, Teku, Kathmandu, Nepal and admitted at tertiary center, Kathmandu Medical College and Teaching Hospital.

Eschar, a localized necrotic skin lesion was present in four patients & was seen in abdomen, lower back and thigh at the site of infecting chigger bite among the observed patients. Eschar on lower back and abdomen region of two different patients shown on Figure 2 and 3 respectively.

All patients were negative for concurrent Dengue IgM, IgG, Malarial Parasite antigen, Brucella antibody test (tube agglutination), Leptospira IgG, IgM and Kalazar antigen.

Thrombocytopenia was present in two patients ($<150,000/\text{mm}^3$) while three patients presented with hypoalbuminemia ($<3.5\text{gm/dl}$).



Fig 2 Eschar on left buttocks.

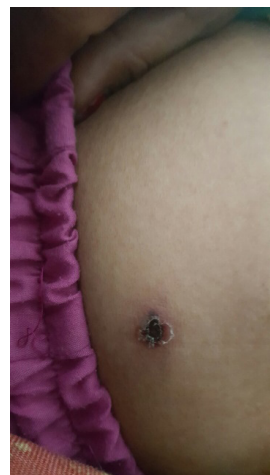


Fig 3 Eschar on abdomen.

Serum Alkaline Phosphatase, serum Alanine Aminotransferase and Aspartate Aminotransferase were elevated in 4 out of 6 patients.

Two patients showed minimal ascites, one had bilateral mild pleural effusion and one had left sided pleural effusion.

Serum Lipase was raised in patient 2 only (993 U/L).

Of the six, all had short ICU stay. Of the six patients two responded to oral Azithromycin 500mg daily course while four required oral doses of Doxycycline 100mg daily. Length of hospital stay was 5.3 ± 1.7 days.

DISCUSSION:

Scrub typhus is widely endemic in South Asian countries including Nepal and has been of a public health concern. It is caused by *Orientia tsutsugamushi*, a rickettsial bacteria and is transmitted by the bite of a Chigger or trombiculid mites larvae¹. The incubation period for Scrub typhus is around 6 to 21 days and usually presents with fever with chills, diaphoresis, lymphadenopathy, headache and myalgia⁶. The site of arthropod bite can present with black eschar or tache noire may be present⁷. From the bite site, the microorganism then spreads through lymphatic fluid and blood, and causes systemic lab abnormalities like transaminitis⁸. Though until 2006, scrub typhus was limited to only the tsutsugamushi triangle, in 2006 there were cases identified in Middle east and Southern Chile⁸.

Scrub typhus is potentially fatal infection in endemic regions if not identified and treated promptly and incidence is nearly around 1 million yearly⁹. Sporadic outbreaks are known to occur in the Indian subcontinent mainly in the monsoon and post monsoon seasons¹⁰.

Mean time from symptom onset, which was fever for all patients in our study, to hospital admission was 12.5 days. This was similar to other studies conducted in India, which showed 2/3rd patient being diagnosed in second week of symptoms onset¹⁰⁻¹⁴.

Eschar was present in four out of six patients, similar rates was found in other studies done in Vietnam, Taiwan and South Korea¹⁵⁻¹⁷. Even though presence of eschar can be an important clue to diagnosis this may not be present in many patients as highlighted in a prospective observational study where 66 patients were studied where eschar was seen in only 12%¹⁰.

Meningoencephalitis has been frequently encountered in previous studies from Indian subcontinent as well, with varied incidence from 3%¹⁰ to 26%¹⁴. Our study had one patient with meningoencephalitis.

Liver enzymes were elevated in 66% of our patients, similarly higher prevalence was seen in other studies done in Indian and Taiwan 95%¹⁴, 95%¹¹, and 81%¹⁶.

50% of our patients presented in septic shock. Similarly high incidence was found in one study in 2002, of the 51 patient studied for septic shock in a seven week period 35% were found to have Scrub typhus infection, With two deaths accounting to respiratory failure and one death to combined respiratory and renal failure¹⁸. Lower rates were found in other studies 3% in Tsay et. Al.¹⁶, and 3.5% in Sinha et. Al.¹¹.

Thrombocytopenia was seen in one third of the patients in our study. Higher rates were seen in Tsay et. Al., 44%¹⁶ and 85% in Sinha et. al.¹¹.

Our study used ELISA for diagnosis of scrub typhus. Immunofluorescence (IFA) remains the gold standard diagnosis, but polymerase chain reaction from blood and eschar skin biopsy can also be used¹⁹.

Doxycycline is the treatment of choice in most patients, whereas rifampin or azithromycin can be used in case of doxycycline resistance²⁰. Though doxycycline has clinical evidence in mild-moderate disease²⁰, our study showed patient with septic shock responding well to doxycycline with rapid improvement in symptoms.

CONCLUSION:

Fever, transaminitis are common symptoms and signs in scrub typhus, and should be suspected with these features in endemic regions even in the absence of typical features like eschar and elevated white blood cell count. Early diagnosis is important as disease can be fatal secondary to septic shock and multi organ dysfunction, and early diagnosis can also decrease length of hospital stay. Though doxycycline has been usually proven in mild and moderate disease, our study had good response to doxycycline even in patients with septic shock, which needs further large-scale studies.

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