



SCRUB TYPHUS: ONE SHOULD BE VIGILANT!!

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ABSTRACT**BACKGROUND:** Humans are opportunistic hosts for scrub typhus which is transmitted by trombiculid mites to rodents.**AIMS:** To study the magnitude of scrub typhus in kumaun region of Uttarakhand in India.**MATERIALS AND METHODS:** All adult patients presenting with febrile illness from March 2015 to November 2015 were evaluated.**OBSERVATIONS AND RESULTS:** A total of 210 patients with undiagnosed fever were included in the study and 98 (46.67%) patients showed presence of IgM antibodies against scrub typhus. The common symptoms were fever, cough, anorexia, myalgias, nausea/vomiting. Out of 98, 41 patients presented with severe scrub typhus. Four (4.08%) patients died due to multi-organ dysfunction syndrome (MODS).**CONCLUSION:** Scrub typhus, if early and appropriately diagnosed, prevents life threatening situations.**KEYWORDS :** Scrub Typhus, Eschar, Orientia Tsutsugamushi, Commercial Elisa Kit**INTRODUCTION**

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi*, also called *Rickettsia tsutsugamushi*. It is transmitted by larval forms (chiggers) of trombiculid mites to rodents, while humans are opportunistic hosts.[1] The infection occurs in diverse habitats like seashore, rice fields and even semi-deserts. [2] This disease is significant as any undue delay in diagnosis and initiation in appropriate therapy can often result in severe complications such as acute respiratory distress syndrome, acute renal failure, meningitis, hepatitis, gastrointestinal bleeding, pancreatitis, myocarditis, septic shock and multisystem organ failure often culminating in death in morbid patients.[3]

Scrub typhus was first reported in Taiwan by Hatori in 1915.[1] It is endemic in so called "tsutsugamushi triangle" which extend from Pakistan, India and Nepal in the west, to south-eastern Siberia, Japan, China and Korea in the north to Indonesia, the Philippines, northern Australia and the pacific islands in the south. In India, the disease had occurred amongst troops during World War II in Assam and West Bengal, and in 1965 Indo Pak war.[4] Although the disease is endemic in our country, it is grossly under diagnosed in the kumaun region of Uttarakhand. So, we decided to study the magnitude of scrub typhus in kumaun region of Uttarakhand and to assess the clinical manifestations and outcome of serologically positive patients.

MATERIALS AND METHODS

All consecutive adult patients presenting with febrile illness from March 2015 to November 2015 were evaluated in government medical college (tertiary centre), Haldwani. Other likely diagnoses such as malaria, leptospirosis, dengue fever, viral pharyngitis, enteric fever, urinary tract infection were ruled out by history, clinical examination and appropriate laboratory investigations. The patients were subjected to a battery of investigations such as complete blood count, platelet count, urine analysis, renal function tests and liver function tests, smear for malarial parasite, rapid antigen test for malaria, serology for leptospirosis and dengue haemorrhagic fever, widal test and blood culture. The patients were subjected to further investigations such as bleeding and clotting time, prothrombin time / International normalized ratio (INR), activated partial thromboplastin time,

fibrin degradation products, chest X-ray, abdominal ultrasonography, wherever necessary. Blood samples (5 ml) were collected and serum preserved at -70°C from patients who remained febrile and no etiological diagnosis could be made. These samples were subjected, retrospectively, in batches, to testing for specific IgM antibodies against *O. tsutsugamushi* using a commercial ELISA kit (InBiOS International Inc. USA). The kit uses *O. tsutsugamushi* derived recombinant antigen mix. The test was performed as per manufacturer's instructions. The study protocol was approved by institutional Ethics Committee and informed consent was obtained from the patients. The patients having IgM antibodies against *O. tsutsugamushi* in their serum samples were diagnosed as having scrub typhus. Various complications such as acute renal failure, hepatitis, ARDS, disseminated intravascular coagulation, pancreatitis, meningitis, myocarditis, etc. were noted.

The following criteria (based on standard definitions given in Harrison's Principals of Internal Medicine) were used to diagnose above complications:(i) Acute renal failure was defined as urine output less than 400 ml/24 h or serum creatinine >1.6 mg% failing to improve after adequate rehydration. (ii) Patients who had elevation of serum bilirubin > 3 mg% and/or elevation of serum transaminases >3 times the upper limit of normal were labelled as having hepatitis. (iii) Acute onset of non-cardiogenic pulmonary edema manifesting with bilateral alveolar or interstitial infiltrates on chest radiograph and PaO₂/FIO₂ <200 mm Hg on arterial blood gas analysis confirmed the presence of ARDS. (iv) Disseminated intravascular coagulation (DIC) was defined as clinical manifestations of bleeding along with thrombocytopenia and elevated coagulation profile (raised fibrin degradation products, prolonged prothrombin time/INR, activate partial thromboplastin time, aPTT). (v) Pancreatitis was defined as acute onset of clinical signs such as abdominal pain, vomiting, guarding/ tenderness associated with elevation of serum amylase/ lipase >3 times upper limit of normal. (vi) Myocarditis was defined as presence of systolic global left ventricular wall motion abnormalities on 2D echocardiography along with ECG changes and clinical findings consistent with left ventricular dysfunction in a previously normal individual. (vii) Systolic blood pressure of <90 mm Hg for at least 1 h despite adequate

fluid resuscitation was labelled as shock. (viii) Meningitis was defined as presence of altered sensorium and signs of meningeal irritation associated with elevated proteins and neutrophilic cytology on CSF analysis.[5]

The patients, who were serologically diagnosed of having scrub typhus or those with strong clinical suspicion of scrub typhus, were given doxycycline in the dosage of 100 mg twice a day for 10 days. All other supportive measures such as haemodialysis, ventilator support, transfusion of blood components, inotropic support were given as per the indications.

RESULTS

A total of 210 patients with undiagnosed fever were included in

TABLE 1- PRESENTING SYMPTOMS AND SIGNS

Symotms	Number (%)	Signs	Number (%)
Fever	98 (100%)	Hepatomegaly	28 (28.6%)
Cough	60 (61.22%)	Icterus	16 (16.32%)
Anorexia	57 (58.16%)	Eschar	8 (8.16%)
Myalgia	24 (25.5%)	Lymphadenopathy	8 (8.16%)
Nausea/vomiting	20 (20.4%)	Oedema	8 (8.16%)
Breathlessness	18 (18.36%)	Decreased urine output	5 (5.1%)
Maculopapular rash	12 (12.24%)		
Altered sensorium	6 (6.12%)		

Among the laboratory parameters, raised transaminases [Serum glutamic oxaloacetic transaminase, SGOT (82%) and Serum glutamic pyruvic transaminase, SGPT (78%)], leukocytosis (66%) and hypoalbuminemia (60%) were the main findings. Thrombocytopenia (30%), raised serum creatinine (20%) and bilirubin (10%) were also encountered.

TABLE 2- LABORATORY FINDINGS

LABORATORY PARAMETERS	PERCENT
SGOT	82%
SGPT	78%
Leucocytosis	66%
Hypoalbuminemia	60%
Thrombocytopenia	30%
Serum creatinine	20%
Serum bilirubin	10%

Forty one (41.8%) patients, out of 98 presented with severe scrub typhus. Acute respiratory distress syndrome, hepatitis and meningitis were seen in 10 (10.2%), 9 (9.2%) and 6 (6.12%) patients respectively. Four (4.08%) patients died due to multi-organ dysfunction syndrome (MODS). In the present study, all patients were treated with doxycycline empirically in the dosage of 100 mg twice a day for 10 days on the clinical suspicion of scrub typhus and nearly all patients responded promptly to treatment.

TABLE 3- COMPLICATIONS

COMPLICATIONS	NUMBER (%)
ARDS	10 (10.2%)
Hepatitis	9 (9.2%)
Meningitis	6 (6.12%)
Renal impairment	4 (4.08%)
MODS	4 (4.08%)
Pericardial effusion	2 (2.04%)
DIC	2 (2.04%)
Deaths	4 (4.08%)

DISCUSSION

Scrub typhus is an acute febrile illness with a diverse variety of signs and symptoms. It should be suspected in patients presenting with high grade fever with or without symptoms and has been in an endemic area. It is a serious health issue

the study and 98 (46.67%) patients showed presence of IgM antibodies against scrub typhus. Out of 98, 58 (59.2%) were males and 40 (40.8%) were females. The common symptoms were fever (100%), cough (61.22%), anorexia (58.16%), myalgias (24.5%), nausea/vomiting (20.4%), followed by breathlessness (18.36%), maculopapular rash (12.24%) and altered sensorium (6.12%). The commonest signs seen were hepatomegaly (28.6%) and icterus (16.32%). Nearly half of patients (40%) had signs suggestive of capillary leak syndrome in the form of generalized anasarca, pedal oedema, hypotension and hypoalbuminemia. The pathog nomic features such as eschar and lymphadenopathy were rare in the present study; only 8 (8.16%) patients had the presence of eschar with lymphadenopathy.

and needs to be differentiated from other causes of febrile illnesses such as malaria, enteric fever, dengue, leptospirosis, infectious mononucleosis etc. The habitat including the vegetations areas and the environmental conditions best suits for presence of scrub typhus organism and the vector in the kumaun region of uttrakhand. Most of the patients belong to the vegetation areas (rice fields) in our study.

The key to diagnosing scrub typhus is finding a typical eschar of approximately 5-20 mm in diameter, which is the result of the insect bite that transmits the pathogen. This is frequently accompanied by regional lymphadenopathy. Characteri stic ally, an eschar is a non-painful ulcer covered by a centrally depressed dark scab and surrounded by a red areola.[1] But in our study only 8 (8.16%) patients had eschar along with lymphadenopathy. This is in concordance with few reports from India in which very few patients were reported to have eschar.[6,7] Contrary to this, eschar was found in 46% and 60% of patients reported from studies done in South Vietnam and Taiwan, respectively.[8,9]

Raised transaminases were the dominant laboratory findings. SGOT and SGPT were raised in 82% and 78% patients respectively, SGOT being more raised than SGPT. Kim et al reported hypoalbuminemia in 16.3% patients;[10] however in the present study it was present in 60% patients. It is postulated that scrub typhus leads to generalized vasculitis which may involve the tissues of any organ systems. This increases the vascular permeability leading to leakage of plasma protein from the blood vessels causing hypoalbuminemia.[11]Min et al have demonstrated intestinal protein loss by measuring the concentrations of -1- antitrypsin in the stool, and that 11 of 14 patients with scrub typhus revealed intestinal albumin loss by 99mTc-human serum albumin (HSA) abdominal scintigraphy.[12]

In our study, 41 (41.8%) patients presented with complications of scrub typhus. ARDS was encountered in 10 patients. Six out of them needed ventilator support and 4 patients died due to MODS. Hepatitis, meningitis and renal impairment were seen in 9 (9.2%), 6 (6.12%) and 4 (4.08%) patients respectively. Other complications which were noticed were pericardial effusion and disseminated intravascular coagulopathy (DIC). Mortality rate was 4% in the present study. However Sneha et al, Jamil et al and Varghese et al reported a moratlity rate of

16.7%, 8.47% and 14% respectively.[4,5,13] Other complications which can be present in scrub typhus are ileus, encephalitis, pleural effusion, pancreatitis, GI bleeding and convulsions. These are reported in the literature and should be kept in mind while evaluating the patient with febrile illness. Chen et al reported two patients with scrub typhus presenting with abdominal pain, in which an unnecessary laparotomy was performed. Thus, accurate diagnosis of scrub typhus may help to avoid unnecessary surgery.[1]

The diagnosis of scrub typhus is generally made on clinical grounds alone. As the clinical symptoms and signs overlap with many infectious diseases, overshadowing is quite common. The cheapest and most easily available serological test is the Weil-Felix test, but this is unreliable. The gold standard is indirect immunofluorescence, but the main limitation is its availability. Rapid bedside kits are available but the availability is severely limited by their cost.[14] In our study, we used a commercial ELISA kit (InBios International Inc. USA) for testing specific IgM antibodies against *O. tsutsugamushi*. The kit uses *O. tsutsugamushi* derived recombinant antigen mix.

CONCLUSION

Scrub typhus is a neglected but treatable disease that may develop serious complications and may even result in death if appropriate treatment is not initiated. Therefore, it should be in the differential diagnosis of every patient presenting with an acute fever along with respiratory symptoms, or renal impairment, or hepatic dysfunction, and/or CNS symptoms. Clinicians must be vigilant, as patients can present with a variety of clinical symptoms, regardless of the presence of fever. Every patient with a suspected *O. tsutsugamushi* infection should be examined thoroughly for eschar lesions, as it is of diagnostic value. If diagnosed early, treatment is effective and a favorable outcome can be expected.

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