Scrub typhus is one of the leading causes of acute febrile illness in India. It is associated with rash and often an eschar, which responds dramatically to antibiotics. In some cases, it results in serious illness leading to multiple organ involvement and finally death. The various clinical manifestations of scrub typhus arise mainly due to systemic vasculitis, caused by direct effects of organism as well as exaggerated immune response. The disease course is often complicated, leading to mortality in the absence of treatment. Here, in this case series, we describe three cases depicting the typical manifestations which a patient of scrub typhus can present with highlighting the fact that high index of clinical suspicion is of utmost importance for this deadly disease.

Key Words: Acute kidney injury, atrial fibrillation, scrub typhus

INTRODUCTION

Scrub typhus is a life-threatening zoonosis caused by Orientia tsutsugamushi (formerly Rickettsia), an obligate intracellular Gram-negative bacterium, which was isolated in 1930. It is transmitted to human beings by the bite of a larval Leptotrombidium mite (chigger).[1] The target cells are the endothelial cells, monocytes, and other cell types, and the disease is associated with vasculitis and endothelial dysfunction. Illness varies from mild and self-limiting to fatal. After an incubation period of 6–21 days, onset is characterized by fever, rash, headache, myalgia, cough, and lymphadenopathy. Fewer than 50% of patients develop an eschar and <40% develop a rash. It is endemic to a geographically distinct region, the so-called tsutsugamushi triangle, which includes Japan, Taiwan, China, and South Korea. It also occurs in Nepal, Pakistan, Papua New Guinea, and Australian states. In India, initial reports appeared in the 1930s,[3] and a large number of cases were identified among troops during World War II in Assam and West Bengal.[3] Lately, it has been reported with increasing frequency from diverse ecologies, initially from southern India and later from the Himalayan belt, the plains of northern India, coastal areas, and even from metropolitan cities.[4] The state of Sikkim situated in the Eastern Himalayas has a total geographic area of 7299 km² and is essentially a mountainous region without flat piece of land of any extent anywhere.

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from a tertiary care teaching hospital in Sikkim, India. These manifestations if present in a patient will help the clinicians in implementing a suspect and treat strategy and initiate proper treatment to prevent serious morbidity and fatality in this potentially treatable and curable disease.

**CASE REPORTS**

Case 1
A 2-year-old male child presented to the Department of Pediatrics of our institute with fever associated with chills for 6 days, decreased urine output for 4 days, progressive abdominal swelling associated with loose stools for 3 days, and nonproductive cough for 2 days and was hospitalized. Physical examination revealed a febrile child with pallor, periorbital puffiness, pedal edema, hepatomegaly, evidence of free fluid in abdomen, and bilateral pleural effusion. Injection ceftriaxone 50 mg/kg/day was given for 3 days empirically along with supportive treatment, but the child did not improve. Antistreptolysin O test was done in order to rule out poststreptococcal glomerulonephritis which was negative. A brownish-black-crusted lesion with surrounding erythema-eschar was found below the left axilla [Figure 1]. Blood samples were sent for routine investigations. Complete blood count (CBC) revealed hemoglobin (Hb) of 9.9 g/dl, Total leucocyte count (TLC) of 6600/mm$^3$, polymorph (85%), and platelets of 90,000/mm$^3$. The urine analysis indicated proteinuria, microscopic hematuria, and red blood cell casts. Blood urea (43 mg/dl) and serum creatinine (1.6 mg/dl) were raised. The liver function tests revealed transaminitis and cholestasis (alanine aminotransferase [ALT] 148 IU/L and aspartate aminotransferase [AST] 161 IU/L). The kidney function also was deranged with sodium (43 mg/dl) and potassium (7.8 mg/dl). The chest X-ray view confirmed bilateral pleural effusion [Figure 2]. Ultrasound (USG) of abdomen and pleural spaces revealed ascites with hepatosplenomegaly and bilateral pleural effusion. Widal test was negative. Hepatitis B virus surface antigen and anti hepatitis C virus were negative. A diagnosis of scrub typhus complicated with acute kidney injury (AKI) was made based on the basis of clinical findings, laboratory results, and positive Weil–Felix test and IgM ELISA. Tablet doxycycline 2.2 mg/kg/day was given for 3 days, and by 6th day of admission, the child became afebrile, with regression of edema and was discharged home on the 10th day.

Case 2
A 53-year-old male presented to the Emergency Department of our Institute with fever, headache, vomiting, and altered consciousness for the last 2 days. The informant was his son with fair reliability. The fever was initially low grade but had become high grade and was associated with chills and rigors. He developed confusion and disorientation a day or 2 days before hospitalization. There was no history of seizures, cough, or dysuria or rashes. He was a known hypertensive

| State                  | Year of study | Number of suspected cases | Number of laboratory-confirmed cases | Eschar (%) | Mortality (%) |
|------------------------|---------------|---------------------------|-------------------------------------|------------|---------------|
| Rajasthan[24]          | 2017          | NA                        | 66                                  | 12         | 21.2          |
| Assam[25]              | 2017          | 511                       | 104                                 | 0          | 49            |
| Uttar Pradesh[26]      | 2018          | 357                       | 97                                  | 0          | NA            |
| Punjab[27]             | 2014          | 772                       | 98                                  | 10.2       | 3             |
| Andhra Pradesh[28]     | 2014-2015     | NA                        | 60                                  | 10         | NA            |
| Meghalaya[18]          | 2011-2012     | 662                       | 90                                  | 11.1       | 38.5          |
| Uttarakhand[29]        | 2015          | NA                        | 284                                 | 17         | 8.5           |

NA: Not available
on regular medications. He was a teetotaler and nonsmoker. On examination, the patient was disoriented to time, place and person, was febrile, and had blood pressure (BP) record of 170/100 mmHg. He did not have any icterus, rashes, or signs of meningeval irritation. Cranial nerve examination revealed no deficit except bilateral papilledema. Other systemic examinations were normal. Investigations revealed normal urine routine examination. CBC revealed TLC of 14,230/cmm polymorph 85%, with normal Hb and platelets. The liver function tests revealed transaminitis and cholestasis (ALT 99 U/L, AST 122 U/L, Gamma glutamyl transferase (GGT) 300 U/L, and alkaline phosphatase of 304 U/L). USG of the abdomen revealed mild hepatosplenomegaly. Chest X-ray view was normal. Leptospira Microscopic agglutination test (MAT) was negative. Noncontrast computed tomography scan of head revealed features of early cerebral edema. Cerebrospinal fluid (CSF) studies revealed glucose 45 mg/dL, protein of 78 mg/dL, cells of 202/cmm with lymphocytic predominance, negative for acid-fast bacilli, and adenosine deaminase of 5 U/L, and GeneXpert was negative. CSF viral antibodies for Herpes simplex virus and Japanese encephalitis were negative. IgM for scrub on day 2 of hospitalization was 1.25 (normal range < 0.14). He was treated with parenteral doxycycline (5 mg/kg twice daily × 7 days), mannitol (100 g/24 h), and levetiracetam (500 mg twice daily × 2 weeks). He improved slowly, and a repeat investigation after 1 week revealed a normal CSF study, a normal MRI brain and an IgM scrub titer of 1.68. He improved slowly but completely and was discharged after total 2 weeks hospitalization.

**Case 3**
A 45-year-old male who was previously well presented to the Emergency Department of our institute with complaints of fever, shortness of breath, and cough with scanty expectoration for the last 7 days. The fever was high grade in nature and was occasionally associated with chills and rigors. He was referred from a nearby private nursing home where he was admitted for the last 3 days. During his stay there, he developed aphasia and shortness of breath. There was no history of any seizure, rashes, weakness, or hematuria. The patient was a chronic smoker for the past 20 years. On examination, he was conscious, alert, and oriented. He was febrile and had a heart rate of 120 beats/min, respiratory rate 44 breaths/min, and BP 90/60 mmHg. The pulse was irregularly irregular. On systemic examination, bilateral coarse crepitations were present in lung bases on auscultation. Other examinations were within normal limits. A provisional diagnosis of acute febrile illness was made with an incidental finding of atrial fibrillation (AF). Cardiology opinion was sought for the same. The patient consent was obtained for Direct current (DC) cardioversion, and a shock of 200 joules was given. The rate was brought in control, but the AF could not be reverted back. Injection amiodarone 150 mg was given immediately and then tapered at regular intervals. Blood samples were sent for routine investigations. CBC revealed TLC of 15,400/cmm polymorph 87%, with normal Hb and platelets. The liver function tests were within normal limits. Dengue serology and malarial antigen came negative. Cultures from blood and urine were sterile. Weil–Felix test was positive and IgM antibody for scrub typhus was strongly positive (by ELISA). The patient was reexamined thoroughly and an eschar was found on the back of the neck confirming the diagnosis [Figure 3]. He was started on tablet doxycycline (100 mg twice a day) for 7 days. He responded to doxycycline, and within 48 h, his symptoms decreased significantly and her vitals steadily improved. The patient's condition improved gradually, and he was discharged after 2 weeks.

**DISCUSSION**
Rickettsial infections are emerging as pathogens around the world in areas which were hitherto unaffected. The rickettsial diseases were once thought to have disappeared from India, but cases are reemerging from several parts of the country. Scrub typhus is now most commonly reported rickettsial infection from the Indian subcontinent. The diagnosis of scrub typhus is made by using Faine's criteria, with proper history, epidemiological data, occupational history, clinical examination, seasonal variation, and laboratory support. In India, scrub typhus cases have been regularly reported from Vellore and Tamil Nadu.[6,7] Darjeeling is one of the endemic areas of scrub typhus until 1960, thereafter no outbreak was there. In 2005, cases are being reported. Sikkim has annual rainfall of 429–666 mm.[8] Vegetation in Sikkim also favors the chiggers to attach with rodents during monsoon season.[9] The outbreaks are associated with the predominance of the vector...
Leptotrombidium deliense, but recently, there has been an important observation L. deliense was missing, and there is emergence of S. ligula, as the primary vector in the outbreak of Kuruseong district of West Bengal.\[10\] Mahajan et al. have reported the presence of eschars in 7%–97% of scrub typhus cases in Japan.\[11\]

Multiple eschars have been reported in a single patient.\[12\] In our case, a diligent search for skin rashes helped in finding an eschar and later helped in diagnosis. The majority of studies regarding rickettsial infections from various parts of the world are based on the adult populations [Table 1].\[13\] There is a paucity of studies regarding the incidence and clinical profile of scrub typhus in children of scrub typhus. Scrub typhus is regarded as a life-threatening disease in children.

The complications of scrub typhus are pneumonia, acute respiratory distress syndrome, acute hepatitis, AKI, meningitis, pancreatitis, acalculous cholecystitis, axonal polyneuropathy, long-segment myelitis, Disseminated intravascular coagulation (DIC), septic shock, and multiple organ dysfunction syndrome.\[14‑17\] In our cases, patients presented with complications with short incubation time. In the Indian scenario, there is a higher case fatality of 14% when presenting with complications.\[17\] In a study conducted in Meghalaya, only 11.1% patients had eschar and 33.3% of patients presented with complications with high mortality.\[18\] There is need to assess for the predictors of mortality such as BP, liver enzymes, platelet count, respiratory effort, and serum urea and creatinine in such scenario. The doubling time for scrub typhus is 9–18 h, so it takes 4 weeks for the culture to become positive.\[19\] Nested Polymerase chain reaction (PCR) from the eschar samples or buffy coat can help in early diagnosis of the disease within the first 3 days of fever onset even before the appearance of antibodies.\[20\]

Rickettsial infections have been overlooked as a cause of AKI, especially in children. A recent retrospective study from Central India did not report any case of AKI in children with Rickettsial infections.\[21\] Several studies have reported lower incidences of AKI ranging from 2% to 10%. According to Yen et al. scrub typhus presented with symptoms of acute renal failure is a rare but a serious condition.\[22\] The mechanism of AKI in scrub typhus is mainly believed to be impaired renal perfusion due to volume depletion or increased vascular permeability. Overall, renal involvement is considered to be a part of multiorgan dysfunction in patients with severe disease.\[4\]

Acute myocarditis is associated with scrub typhus more common than previously reported. Patients with high bilirubin and paroxysmal AF are at increased risk of acute myocarditis with scrub typhus, and hence, these patients should be evaluated for cardiac complications when presented with scrub typhus.\[23\] The management includes supportive therapy intravenous fluid replacement therapy, mechanical ventilation, and intravenous antibiotics, with the addition of tablet doxycycline 100 mg twice daily for 7 days.\[24‑29\]

**CONCLUSION**

Scrub typhus has been underdiagnosed in India due to its nonspecific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of diagnostic facilities. The clinical manifestations of scrub typhus in children are nonspecific and are likely to be misdiagnosed. Scrub typhus does not find a mention in most descriptions of tropical community-acquired AKI or acute myocarditis. Considering the reemergence of scrub typhus in India, patients presenting with fever and AKI as well as rhythm abnormalities should be investigated for scrub typhus. Early diagnosis of scrub typhus and the initiation of empirical therapy with doxycycline will reduce patient morbidity and mortality.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the preparation of this report.

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**Conflicts of interest**

There are no conflicts of interest.

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