

Multifaceted realities of scrub typhus: a case series from southern India

Diviya Bharathi Ravikumar¹, Barath Prashanth Sivasubramanian²,
Sruthi Nandhaa Shanmugam³, Vanitha Krishnaswamy⁴, Ali Rabaan^{5,6,7},
Jaffar A. Al-Tawfig^{8,9,10}, Raghavendra Tirupathi¹¹

¹Department of Internal Medicine, ESIC Medical College and PGIMS, Chennai, India;

²Department of Infectious Diseases, University of Texas Health Science Centre, San Antonio, USA;

³Department of Internal Medicine, Kasturba medical college, Mangalore, India;

⁴Department of Pediatrics, KAPV Government Medical College, Trichy, India;

⁵Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia;

⁶College of Medicine, Alfaisal University, Riyadh, Saudi Arabia;

⁷Department of Public Health and Nutrition, The University of Haripur, Haripur, Pakistan;

⁸Specialty Internal Medicine and Quality Department, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia;

⁹Infectious Diseases Division, Department of Medicine, Indiana University School of Medicine, Indianapolis, USA;

¹⁰Infectious Diseases Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA;

¹¹Cure Drug Repurposing Collaboratory

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SUMMARY

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*, a Gram-negative bacillus, commonly occurring in the Asia-Pacific region. It is transmitted to humans by the bite of an infected *Leptotrombidium mite* and the bacterium causes endothelial dysfunction resulting in widespread vasculitis and the possible development of thrombocytopenia, meningitis, acute respiratory distress syndrome, and infrequently, myocarditis. Early diagnosis and prompt treatment are crucial in managing scrub typhus. Here, we present four cases of scrub typhus with a comprehensive literature review. This study highlights the significance of considering scrub typhus as a possible diagnosis in patients of all ages from endemic regions who exhibit symptoms such as fever, thrombocytopenia, or transaminitis, even in the absence of typical clinical features.

Two cases exhibited the characteristic lesion of eschar at the site of mite feeding. One case involved a middle-aged woman who was diagnosed with typhus-induced myocarditis with left ventricular dysfunction. Another case involved a 23-day-old neonate with poor feeding and seizures, who was diagnosed with late-onset sepsis with meningitis. Scrub typhus was confirmed in all cases using a positive qualitative IgM ELISA. However, it is preferred to use paired (ELISA before and after antibiotic therapy) or quantitative titers for confirmation. Healthcare providers must consider the patient's exposure history and clinical presentation to diagnose and treat scrub typhus promptly.

Keywords: Myocarditis, scrub typhus, meningitis, eschar, mite bites.

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi* discovered in 1930), is a bacterial infection transmitted to hu-

mans through the bite of an infected mite of the genus *Leptotrombidium*, commonly known as chiggers. Chiggers serve as the bacterium's reservoir, and the infection is mostly prevalent in South and East Asia and parts of the Pacific Rim [1, 2]. The two major categories of vertebrates that carry chiggers are the "maintaining hosts," including rodents, shrews, and ground-dwelling birds, and the "incidental hosts," which include other birds and larger mammals such as humans [3]. In Asia,

Corresponding author

Barath Prashanth Sivasubramanian

Email: barathprashanth18196@gmail.com

the seasonality of human scrub typhus has been well documented. Japan, South Korea, Taiwan, and northern parts of China report the infection almost exclusively occurring from spring until early winter. Thailand, Burma, and India have found the disease to be most prevalent from June to November but may occur year-round [4].

Scrub typhus has been on the rise recently, with an estimated 1 million cases occurring annually [5]. Hospitalization is required for about a third of cases due to the involvement of multiple organs and is associated with high fatality rates [6]. According to a study conducted in India, 24.4% of patients with unexplained fever with or without multi-system involvement were found to have scrub typhus, and 53.1% of those with scrub typhus had acute kidney injury [7]. Scrub typhus, if left untreated, has a mortality rate of around 6%, rising to 13% when appropriate antibiotics are not used. Complications can lead to higher mortality

rates, with 14% in case of central nervous system infection and 20% in case of multiple organ [8]. The most common complications include hepatitis (40.5%), thrombocytopenia (28.4%), acute respiratory distress syndrome (ARDS) (20.5%), acute kidney injury (19.2%), meningitis (16.4%), shock (16.2%), and myocarditis (15.5%) [6]. Thus, in this study, we present four cases to illustrate the varying presentations and complications of scrub typhus.

Case Presentation - 1

A 45-year-old woman from South India presented to a primary care facility with a two-day history of intermittent fever, headache, severe vomiting, lower abdominal pain, and loss of appetite. On room air, her SpO₂ was 98%, body temperature was 39°C, blood pressure was 120/80 mm Hg, pulse rate was 101 beats per minute, and respiratory rate was 20 breaths per minute. The patient's

Table 1 - Laboratory values at the time of admission.

	Case - 1	Case - 2	Case - 3	Case - 4
Parameters	Values	Values	Values	Values
Hemoglobin	11.2 g/dL	12.2 g/dl		9 g/dL
White Blood Cell count	11,430/mm ³	14200/mm ³	23,000/mm ³	6,980/mm ³
Differential count	N 80.6%, L 15.7%, M 3.4%, E 0%, B 0%		N 63%, L 35%, E 1%, M 1%, B 0%	N 59.1%, L 34.2%, M 2.9%, B 0.4%, E 0.1%
Platelet Count	150,000 cells/L	87000 cells/L	75,000 cells/L	120,000 cells/L
Blood Urea Nitrogen	18.3 mg/dL	72 mg/dL		8.12 mg/dL
Serum Creatinine	0.87 mg/dL	1.8 mg/dL		0.71 mg/dL
Aspartate Aminotransferase	129 U/L	30 U/L		75 U/L
Alanine Aminotransferase	70 U/L	26 U/L		158 U/L
Alkaline Phosphatase	57 U/L			55 U/L
Sodium		136 mEq/L		
Potassium		4.2 mEq/L		
Total Bilirubin	1.670 mg/dL	0.8 mg/dL		0.863 mg/dL
Serum Glucose	154 mg/dL	136 mg/dL		99 mg/dL
C-reactive protein	3.5 mg/dL	4.2 mg/dL		20.9 mg/dL
Urine Analysis	Trace albumin and 20 to 25 pus cells/HPF			
ESR				22 mm/hr
Blood culture			No growth	
Smear for malarial parasites			Negative	
Blood Widal			Negative	

Figure 1
An eschar
with
surrounding
inflammation
on the right
suprascapular
area



qSOFA score was 0, indicating she was not at high risk of sepsis. The patient had mild anemia (hemoglobin 11.2 g/dl), neutrophilic leukocytosis (WBC - 11,430/mm³), elevated liver enzymes (AST - 129 U/L, ALT - 70 U/L), and ongoing inflammation (CRP levels of 3.5 mg/dL).

The chest radiograph showed no abnormalities, while ECG indicated sinus tachycardia. Testing revealed negative for dengue, malaria, and typhoid. In view of her symptoms and neutrophilic leukocytosis, a bacterial etiology was presumed, and was started on intravenous ceftriaxone. Her condition did not improve and was transferred to the tertiary care facility on the fourth day of illness. Patient had temperature of 39 degrees

C, 108 beats per minute, her saturation was well maintained, and respiratory rate was 17 breaths per minute. On further probing, the patient revealed a history of insect bite on her back. On examination, 2 x 1 cm eschar with surrounding inflammation was found on the right suprascapular area (Figure 1).

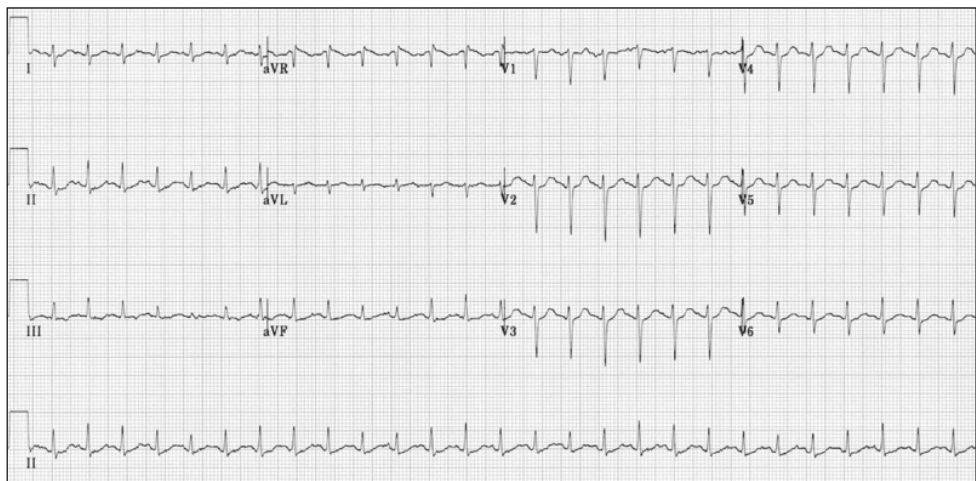
ELISA yielded positive results for IgM scrub typhus and negative results for IgG scrub typhus and leptospirosis. PCR testing for COVID-19 was also negative. Due to the patient's prolonged fever and decreasing platelet count, an ultrasound of the abdomen was performed, which revealed mild splenomegaly measuring 12.3 cm and grade 1 fatty liver.

After the diagnosis of scrub typhus was confirmed, the patient met the criteria for systemic inflammatory response syndrome (SIRS) (heart rate of 108 beats per minute, temperature of 39°C). She was admitted to the general medical ward, ceftriaxone was discontinued, and intravenous doxycycline was added. As the patient met the criteria for SIRS, intravenous route was chosen. Two days after starting antibiotics, the patient's fever subsided, and was changed to oral doxycycline 100 mg twice daily for five days. The patient was given analgesics and antiemetics to alleviate the symptoms, and she was discharged following symptomatic improvement.

Case Presentation - 2

A 45-year-old female presented to the emergency department with a five-day history of fever asso-

Figure 2
EKG of Myocarditis



ciated with vomiting and breathlessness for three days. She also complained of orthopnea and had an eschar on her lower abdomen that was noticed a week ago.

On examination, the patient was conscious and cooperative. Her blood pressure was 130/90 mm Hg, pulse was 120/min, and her oxygen saturation was 93% with nasal oxygen at 4 liters/min. Basal crepitations were noted over the lung fields. An eschar was present on her right lower quadrant of the abdomen. She had pitting pedal edema on both legs. Jugular vein was not distended.

Further investigations revealed a decreased platelet count and elevated blood urea nitrogen and creatinine on admission. An ultrasound of the kidneys revealed increased cortical echoes bilaterally, indicating inflammation. An IgM ELISA for scrub typhus was positive. Her chest x-ray, liver function tests, and electrolyte levels were within normal limits. The patient had non-specific ST and T wave changes in V2 to V5 in EKG.

An ECHO showed global hypokinesia of the left ventricle, grade 3 left ventricular diastolic dysfunction, severe left ventricular systolic dysfunction

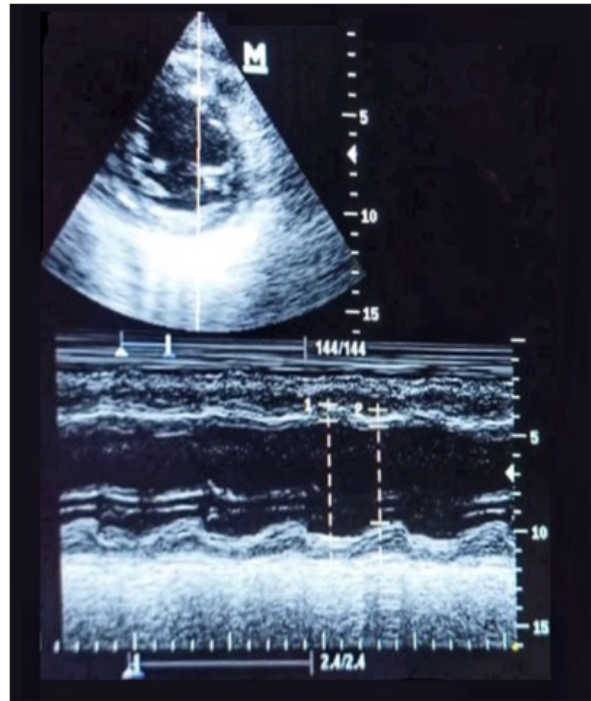


Figure 3 - Echocardiography findings.

Table 2 - Echocardiography findings - Before and After treatment.

	Before Treatment	After Treatment
Left Ventricle	Dilated Global hypokinesia (AW > IW) Grade 3 LV diastolic dysfunction Severe LV systolic dysfunction	No regional wall motion abnormalities Grade 1 LV diastolic dysfunction
Left Atrium	Mitral annular calcification present	Mitral annular calcification present
LVID (S)	49 mm/m ²	28 mm/m ²
LVID (D)	60 mm/m ²	40 mm/m ²
Ejection Fraction	30%	64%
Right Ventricle	RV dysfunction present	No RV dysfunction
Aortic Valve	Sclerosis present Trivial aortic regurgitation No aortic stenosis	Sclerosis present Trivial aortic regurgitation No aortic stenosis
Mitral Valve	Mild mitral regurgitation - No mitral stenosis	Mild mitral regurgitation - No mitral stenosis
PAH	Mild	Mild
Tricuspid	Mild tricuspid regurgitation	Mild tricuspid regurgitation
TAPSEE	8 mm	8 mm
TRPG	40 mm Hg	34 mm Hg
PE	Mild PE	Mild PE
IVC	Normal Size	Normal Size

Legend: LVID (S) - Left ventricular internal dimension in systole. LVID (D) - Left ventricular internal dimension in diastole. AW - Anterior wall. IW - Inferior wall. PAH - Pulmonary arterial hypertension. TAPSE - Tricuspid annular plane systolic excursion. TRPG - Tricuspid regurgitation peak gradient. PE - Pulmonary embolism. IVC - Inferior vena cava.

tion, and an ejection fraction of 30 percent. Right ventricular dysfunction was also noted. No associated valvular conditions were present. Table 2 shows the Echocardiography findings found before and after treatment and figure 3 show the Echocardiography image.

A diagnosis of Scrub typhus causing myocarditis was made. The patient was treated with Doxycycline 100 mg iv twice daily and Dexamethasone 4 mg iv twice daily, and analgesics. Following treatment, the patient's condition significantly improved within a week, and the steroids were tapered off. A repeat ECHO performed after her recovery showed no regional wall motion abnormalities, Grade 1 LVDD, no right ventricular dysfunction, and an ejection fraction of 64%.

Table 3 - CSF studies.

Parameters	Values
Color of fluid	Clear
Cell count	Few neutrophils identified
Protein	40 mg/dl
Glucose	38 mg/dl
Culture	No growth

Case presentation - 3

A 23-day-old neonate presented with poor feeding, lethargy, and fever for three days and a history of clonic seizures on the third day. On examination, the child was febrile, irritable, and had hepatosplenomegaly with ongoing seizure activity. No pallor, icterus, edema, eschars, or purpura were observed. Vital signs included a heart rate of 148/min, respiratory rate of 46/min, and temperature of 37°C. The abdomen was distended with hepatosplenomegaly. Lab tests revealed leukocytosis and thrombocytopenia with a third spacing of fluid evident on chest x-ray and ultrasound. The qualitative CRP was positive, and the ELISA IgM scrub test was positive. A lumbar puncture showed neutrophilic predominance, leading to a diagnosis of late-onset sepsis with meningitis due to bacteremia.

Treatment involving antiepileptics and intravenous doxycycline was given for seven days. The baby responded well to treatment with no recurrence of seizures after the second day. Symptoms subsided by the third day and the neonate regained normal activity by the fourth day. Patient was discharged successfully on the seventh day after completion of the course.

Table 4 - Literature review on Atypical Presentations of Scrub Typhus.

Author	Year	Patient population	Symptoms and signs	Testing methodology
Watanabe et al. [10]	2021	A 63-year-old male patient with hypertension.	Prolonged fever, pharyngeal discomfort, and a mild headache. Rash after administration of amoxicillin hydrate.	Immunofluorescence antibody technique and polymerase chain reaction (PCR) for scrub typhus
Hyoung et al. [11]	2020	A 52-year-old man with hypertension and diabetes mellitus (type II).	Bilateral symmetrical purpura, fever, eschar, proteinuria. A biopsy of purpura demonstrated leukocytoclastic vasculitis and IgA deposition in dermal vessels (henoch schonlein purpura).	O. tsutsugamushi IgA titer, PCR for O. tsutsugamushi, and biopsy of purpuric rash.
Li et al. [44]	2019	A 43-year-old female is from China and is a sanitation worker.	Skin infection, sore throat with fever, dizziness, multi-organ dysfunction syndrome, and immune thrombocytopenia.	Serology for scrub typhus was negative. Treatment was started based on the clinical symptoms with IV piperacillin tazobactam and doxycycline and switched to oral moxifloxacin and doxycycline.
Das et al. [54]	2021	32-year-old woman	Signs of raised intracranial tension, maculopapular rashes, eschar over the right thigh, nuchal rigidity, bilateral papilledema	Presence of IgM antibody in serum, CT scan for cerebral edema, MRI, Magnetic resonance venogram, Cerebrospinal fluid (CSF) analysis Treatment with oral doxycycline, anticoagulants, antipyretics, and IV saline

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<i>Author</i>	<i>Year</i>	<i>Patient population</i>	<i>Symptoms and signs</i>	<i>Testing methodology</i>
Chaturvedi et al. [38]	2016	14-year-old girl	Presented with a 12-day history of high-grade intermittent fever w/ moderate right upper quadrant pain abdominal pain for seven days, SpO2 94%, eschar mark on the left cheek, epigastric pain	Treated with antipyretics, antibiotics (IV ceftriaxone, oral doxycycline), and IV fluids.
Bhattarai et al. [43]	2020	45-year-old male	Fever, right flank pain, burning micturition, decreased platelets, raised creatinine	Presence of IgM antibody in serum. Doxycycline given.
Venketesan et al. [35]	2019	52-year-old Indian lady with diabetes	Presented with fever, rigors, vomiting, headache, bilateral leg pain, myalgia, urinary incontinence, drowsy, and slurred speech	Empirical treatment with ceftriaxone, then meropenem, and then oral doxycycline on day six after serology confirmed scrub typhus
Gupta et al. [36]	2020	26-year-old Indian woman	Diffuse headache, intermittent high-grade fever, chills, rigors, dizziness, imbalance, vomiting, slurring of speech	Scrub serology by ELISA positive for IgM. MRI normal IV fluids, antipyretics, oral doxycycline
Koti et al. [55]	2015	26-year-old Indian male	Fever, breathlessness, tachycardia, restlessness, myoclonic jerks, head titubation, saccadomania	Brain MRI, CSF, IgM titers Doxycycline
Ki et al. [16]	2018	54-year-old woman/ housewife	Myalgia in upper and lower limbs, edema, fever, eschar on the right shin	Pericardial fluid analysis and cardiac MRI to confirm the diagnosis, oral doxycycline, IV fluids to treat
Cho et al. [56]	2019	67-year-old man/farmer	Fever and skin rash, multiple erythematous macules on neck, trunk, and both proximal extremities, two pea-sized eschars found on left axilla and right upper abdomen	Serology using indirect immunofluorescence assay, ECG Oral doxycycline
Kariyawasam et al. [57]	2019	33-year-old pregnant woman	High spiking fever, body aches, myalgia, frontal headache, generalized maculopapular rash, impaired hearing	CSF analysis, audiometry studies, virology screens, weil felix test, final confirmation w/serology high IgG titers Oral azithromycin
Venketesan et al. [35]	2019	52-year-old woman who is a diabetic	Loin pain, dysuria, fever and urinary incontinence	ECG, Blood and urine cultures, Ultrasonogram, IgM serology Empiric treatment with IV ceftriaxone, IV fluids, insulin, Acetaminophen, multivitamins, pantoprazole, switched to IV piperacillin/tazobactam and fluconazole and amitriptyline then switched to IV meropenem and linezolid and finally oral doxycycline after diagnosis
Li et al. [44]	2019	43-year-old Chinese woman	Skin infection, sore throat, fever, dizziness, eschar on right side of neck, decreased urine volume	Chest radiographs, CT, bedside continuous renal replacement therapy Oral doxycycline given.
Dixit et al. [58]	2020	38-year-old lady	Fever, chills, headache, bilateral decrease in hearing, and dizziness	Chest radiograph, abdominal ultrasound, audiometry, serology Empiric IV ceftriaxone followed by oral doxycycline

Case Presentation - 4

A 38-year-old woman from South India presented to the emergency department with a four-day history of intermittent fever, body pain, headache, multiple episodes of vomiting, and abdominal pain. No eschar was found in the scalp, face, mucous membranes, wrists, ankles, palms, and soles. On room air, her SpO₂ was 98%, body temperature was 99.6°F, blood pressure was 110/70 mm Hg, pulse rate was 98 beats per minute, and respiratory rate was 18 breaths per minute. The patient's qSOFA score was 0, indicating she was not at high risk of sepsis. On admission, the lab values indicate anemia (hemoglobin-9 g/dl), active inflammation (CRP - 20.9, ESR - 22 mm/hr), platelet count was 120,000/L, and occult stool blood was positive. The chest radiograph was normal. ECG showed a sinus rhythm of 75 beats/min. ELISA assay was positive for IgM Scrub typhus. The patient's prolonged fever with abdominal pain prompted an abdomen ultrasound, which revealed mild splenomegaly of 13.2 cm and a right ovarian follicular cyst. After the diagnosis of scrub typhus, the patient was admitted and was started on intravenous doxycycline twice daily for two days. Due to repeated episodes of vomiting, an intravenous route was preferred. Following improvement of symptoms, oral doxycycline was given twice daily for five days. The fever subsided on the 6th day and the patient became asymptomatic.

■ DISCUSSION

In the cases described, the patients presented with fever and other symptoms, including vomiting, headache, abdominal pain, breathlessness, poor feeding, lethargy, and seizures. The patients had various clinical syndromes associated with Scrub typhus infections. Investigations involved ELISA for scrub typhus, chest X-ray, ultrasound, and ECHO. Treatment involved doxycycline and supportive therapy for symptom relief. The patients responded well and showed clinical improvement. Scrub typhus can have varying clinical presentations, from mild to severe, including organ failure and death. Symptoms can begin insidiously or abruptly, including fever, intense headache, diffuse myalgias, and a possible rash or eschar. In patients with scrub typhus, the frequency of eschars is highly variable. In one report, 46% of

patients in South Vietnam developed eschars [9]. The development of vasculitis and lymphocytic infiltration of blood vessels in scrub typhus may result in atypical clinical manifestations. Rashes similar to infectious mononucleosis and Henoch schonlein purpura have been reported [10, 11].

According to a study by Varghese et al., the occurrence of cardiovascular complications was seen in 42% and neurologic manifestations in 20% of patients with scrub typhus [12]. Myocarditis, in particular, is rare (1.6%) among scrub typhus patients [13]. These patients are usually elderly individuals (OR=1.04, 95%CI: 0.99-1.09) and had longer hospital stays (OR=1.17, 95% CI: 0.98-1.40) [14]. An elevated total bilirubin level, the incidence of ST elevations on EKG, and paroxysmal atrial fibrillation are more common in those with acute myocarditis than those without [15]. Myocarditis has presented along with rhabdomyolysis [16] and scrub typhus can also cause pericarditis [17] and fulminant perimyocarditis [18]. With regards to ECG changes, abnormalities were identified both in the febrile and convalescent stages of the illness [19]. Studies reported that clinical examination findings at presentation cannot truly reflect on the hemodynamic changes of the patient and ECG is required in scrub typhus [20, 21]. Second-degree heart blocks, relative bradycardia, prolonged QT interval, atrial fibrillation, and ischemic changes have been noted [20, 22-24]. New onset atrial fibrillation is rare (incidence of 1%) and commonly seen in elderly males who have an underlying cardiovascular disease [25, 26]. The ischemic changes in scrub typhus (incidence of 15.1%) are due to bacteria-induced vasculitis and present with no evidence in coronary angiography [23, 27]. Biomarkers such as cardiac troponin, CK-MB, and Brain natriuretic peptide are found to be elevated, and reduced EF is detected [28]. Chest radiography findings have also shown significant associations in patients with cardiovascular dysfunction and must be performed routinely [29].

When encountering any acute febrile illness presenting with an acute onset neurological disorder in the tropics or subtropics, scrub typhus infection should be considered as one of the differentials [30]. Scrub-induced vasculitis, direct bacterial invasion into the CSF, and type 2 hypersensitivity reaction targeting self-antigens are the most common mechanisms by which CNS manifestations occur [31]. A clinically detectable neurological

involvement is seen in 20% of patients, seizures in 6.3–21.6% [32], and meningoencephalitis in 12.4% [33]. In India, 25% of acute encephalitic syndromes are due to scrub typhus [32]. Rarely, scrub typhus can cause cerebral venous thrombosis [34], sudden bilateral sensorineural hearing loss [35], cerebellitis [36], and Guillain barre syndrome [37]. Organ involvement presenting as lobar pneumonia [38], ARDS [39], liver dysfunction [40], pancreatitis [41], acute kidney injury [42], and pyelonephritis [35, 43] have occurred. Furthermore, atypical presentations such as rhabdomyolysis [16], immune thrombocytopenia with multi-organ dysfunction [44], disseminated intravascular coagulation [45], and even hemophagocytic syndrome [46] have been noted.

A conclusive diagnosis of acute scrub typhus infection is obtained using the immunofluorescent antibody (IFA) assay. In situations where there is a lack of trained personnel and fluorescent microscopes, the use of recombinant 56KDa TSA in Scrub typhus IgM ELISA could be a viable alternative to IFA [47]. According to Coleman et al, the utilization of r56KDa TSA in IgM ELISA resulted in a sensitivity and specificity of 93.0% and 94.0%, respectively [48]. In a separate study conducted in India, the sensitivity and specificity of IgM ELISA were reported as 86.5% and 97.5%, respectively [49]. Antibiotics like doxycycline, rifampicin, and azithromycin are commonly used to treat scrub typhus patients, with doxycycline being the drug of choice. Treatment usually involves administering doxycycline at 100mg twice daily for 7-15 days or chloramphenicol 500 mg four times daily orally for 7-15 days [26]. Azithromycin may also be an alternative, especially for pregnant women, 500mg orally for three days [50]. According to a study by Varghese et al., a 7-day intravenous course of doxycycline and azithromycin was superior to either treatment alone in terms of death on the 28th day, persistent complications on the 7th day, or persistent fever on the 5th day (33% vs 47%). The time until PCR negativity was also shorter in the combination group [12]. A study in South India showed the case fatality rate of the disease to be as high as 12.2% [52]. The disease's mortality is attributable to late presentation, delayed diagnosis, and drug resistance [53]. A high index of suspicion and a detailed history, including recent travel and the presence of rash, help establish the diagnosis and reduce mortalities [36, 51].

■ CONCLUSION

In conclusion, Scrub typhus, a disease transmitted through mites, requires a high index of suspicion in endemic areas. Serology using paired quantitative titers is an advised method for diagnosis. Early identification and prompt initiation of antibiotics can significantly reduce the risk of complications associated with this disease. Therefore, healthcare providers and public health officials in endemic regions must prioritize increasing awareness and implementing effective diagnostic and treatment strategies to reduce the morbidity and mortality associated with Scrub typhus.

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