Case Report

Scrub Typhus Complicated by Acute Respiratory Distress Syndrome and Multiorgan Failure; an Unrecognized Alarming Entity in Central India: A Report of Two Cases

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Abstract

Scrub typhus is an acute infectious illness, distributed throughout the Asia Pacific rim. In India, it has been reported from northern, eastern, and southern India. However, cases of scrub typhus have not been well-documented from Vidarbha, an eastern region of Maharashtra state in central India. We report two cases of complicated scrub typhus from Vidarbha region. These cases admitted in unconscious state with 8-10 days history of fever, body ache, cough, and progressive breathlessness. The diagnosis in both cases was based on presence of eschar, a positive Weil-Felix test, and a positive rapid diagnostic test (immunochromatographic assay). Both cases were complicated by acute respiratory distress syndrome (ARDS) and multiorgan failure. Both of them presented in their 2nd week of illness and died during the hospital course in spite of intensive supportive care. The main cause of mortality was delayed referral leading to delay in diagnosis and treatment.

Keywords: Acute respiratory distress syndrome, complications, diagnosis, scrub typhus, treatment

Introduction

Scrub typhus is an acute febrile infectious disease caused by *Orientia tsutsugamushi*, which is an obligate, intracellular gram negative coccobacilli. It is a zoonotic disease caused by rickettsial organisms and transmitted to man by the bite of arthropod vector (mite or chigger). It exists as zoonoses in nature between certain species of mites and rodents as mammalian reservoirs. It is accidentally transmitted to humans. It is distributed over a wide area bound by Japan in the east; through South Korea, China, Taiwan, The Philippines, Thailand, Malaysia, and tropical Australia in the south; and west through India, Pakistan, Tibet to Afghanistan, and southern parts of Russia in the North.[1]

Common clinical manifestations of scrub typhus include fever, generalized lymphadenopathy, cough, breathlessness, myalgia, headache, rashes, eschar formation, anorexia, vomiting, and abdominal pain. Meningoencephalitis, glomerulonephritis, acute renal failure (ARF), interstitial pneumonia, acute respiratory distress syndrome (ARDS), acute hepatic failure, myocarditis, pericarditis, gastrointestinal bleeding, septic shock, acute hearing loss, acute cholecystitis, and intracranial hemorrhage are the unusual complications of scrub typhus reported in the literature.[2-4] The mortality rate of scrub typhus reported in the previous literature was 6.1-30%.[2,3] The clinical presentation varies from mild illness to severe life-threatening illness with multiple organ involvement. Cases of scrub typhus have not been well-documented from Vidarbha, an eastern region of Maharashtra state situated in central India. We present here two cases of scrub typhus complicated by ARDS and multiple organ failure from Vidarbha region. The purpose of reporting these cases of scrub typhus is to make primary care physicians aware of this underrecognized or unnoticed entity. Its early recognition and prompt treatment with doxycycline at the primary care could prevent fatal complications.

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Case Reports

Case 1

A 57-year-old man, resident of Burgaon village, Wardha district,

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farm laborer by occupation was admitted in unconscious state with cough and progressive breathlessness, which developed 3 days prior to admission. He had history of fever and body ache for last 8 days. He had four episodes of generalized tonic clonic seizures within 2 days prior to admission. On general physical examination, he was febrile (39.6°C), anicteric, and drowsy. He had pulse of 108 beats per min, blood pressure of 120/80 mmHg, and respiratory rate of 18 breaths per min. Lymph nodes were not enlarged. A 1 cm sized black crusted ulcer (eschar) was found on the left groin [Figure 1]. The Glasgow Coma Score (GCS) was 8: Eye opening, verbal response, and motor response were 2, 4, and 2, respectively (E2M4V2). His neurological examination revealed no neurological deficit. Bilateral plantar were not elicitable. The pupils were equal and normally reactive to light. No signs of meningial irritation were present. Fundus examination and other system examination revealed no abnormality.

Examination of peripheral blood smear failed to demonstrate malarial parasite. Rapid malaria antigen test (histidine-rich protein 2 (HRP2) and plasmodium lactate dehydrogenase (pLDH)) was negative. His hemogram showed a total leukocyte count (TLC) of 12,200 mm^3 (with differential of 70% polymorphonuclear leukocytes, 22% lymphocytes, and 7% monocytes), hemoglobin of 11.7 gm/dl, and platelet count of 179,000 mm^3. The cerebrospinal fluid (CSF) examination revealed: Normal cellularity, raised protein (115 mg/dl), and glucose (87 mg/dl). There was no organism in gram and Ziehl-Neelsen staining of the CSF. Other laboratory test results were, aspartate aminotransferase (AST), 132; alanine aminotransferase (ALT), 168; total bilirubin, 1.8 mg/dl; albumin, 2.8 gm/dl; total protein, 6.4 gm/dl; creatinine, 4.4 mg/dl; urea, 118 mg/dl; sodium, 125 mEq/l; and potassium, 6.4 mEq/l. Abdominal ultrasonography (USG) revealed no obvious abnormality.

Doxycycline 100 mg twice daily and azithromycin 500 mg once daily were started. Serologic tests were negative for dengue, leptospirosis, and human immunodeficiency virus (HIV). The Widal agglutination test was also negative. His Weil-Felix test was positive for the OX-K antigen in titers of 1:160. Rapid detection kit for scrub typhus (a solid phase immunochromatographic assay) was positive for antibodies to *O. tsutsugamushi*. His computed tomography (CT) head did not reveal any abnormality.

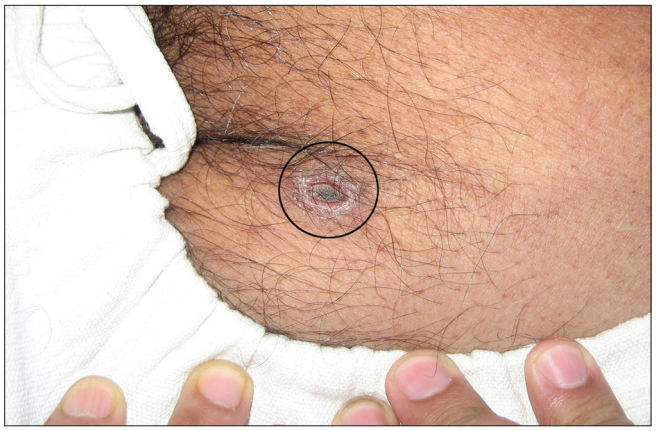

Figure 1: Eschar on the left groin

On the 2nd hospital day, his respiratory distress was increased. His chest examination revealed bilateral diffuse crackles. While the patient was on supplemental oxygen, arterial blood gas analysis revealed a pH of 7.302; $PaCO_2$, 23 mmHg; PaO_2, 51 mmHg; HCO_3^-, 11.4 mEq/L; and PaO_2/FiO_2 ratio of 60 (partly compensated metabolic acidosis). In view of his hypoxemic respiratory failure (arterial oxygen saturation < 90%), he was intubated and put on mechanical ventilator. Chest radiograph showed bilateral diffuse fluffy infiltrates [Figure 2]. A central venous line was setup for monitoring his central venous pressure and fluid replacement in view of hypotension. As his blood pressure did not respond to fluids, inotropes (noradrenalin and dopamine) were added. A final diagnosis of scrub typhus with ARDS, ARF, encephalitis, and septic shock was made. The patient died on the 3rd hospital day in spite of intensive supportive care and antibiotic coverage.

Case 2

A 40-year-old female from Ralegaon village, Yavatmal district, farm laborer by occupation was admitted in drowsy state with history of fever for 10 days, cough and progressive shortness of breath for last 5 days, and pain in right side of abdomen and vomiting for last 3 days. On general physical examination, she was febrile (39.2°C), icteric, and drowsy. She had pulse of 114 beats per min, blood pressure of 110/80 mmHg, and respiratory rate of 26 breaths per min. Her GCS score was E2M5V4. A 1.5 cm sized black crusted ulcer (eschar) was found on the lateral aspect of right thigh [Figure 3]. Her chest examination revealed bilateral crackles. Chest radiograph showed bilateral diffuse infiltrates [Figure 4]. She was treated with oral doxycycline 100 mg twice a day. Arterial blood gas analysis revealed metabolic acidosis and PaO_2/FiO_2 ratio of 54. In view of her respiratory distress, she was intubated and put on mechanical ventilator.

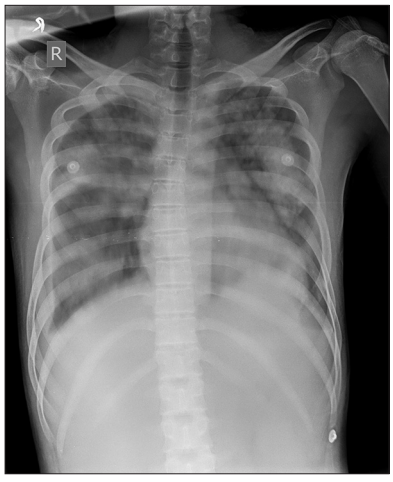

Figure 2: Chest radiography showed bilateral diffuse fluffy infiltrates (case 1)

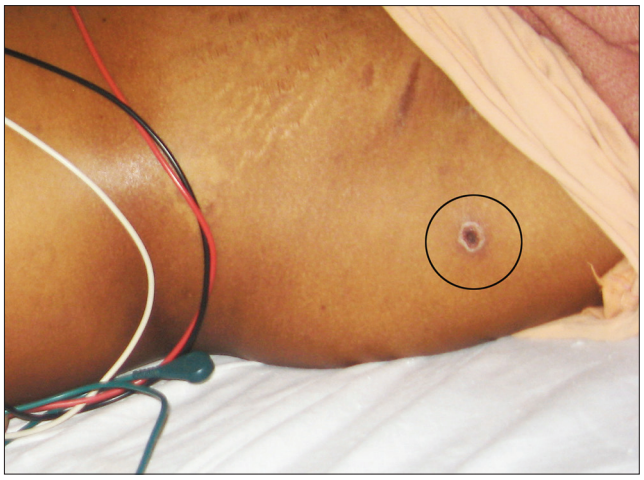

Figure 3: Eschar on the lateral aspect of right thigh

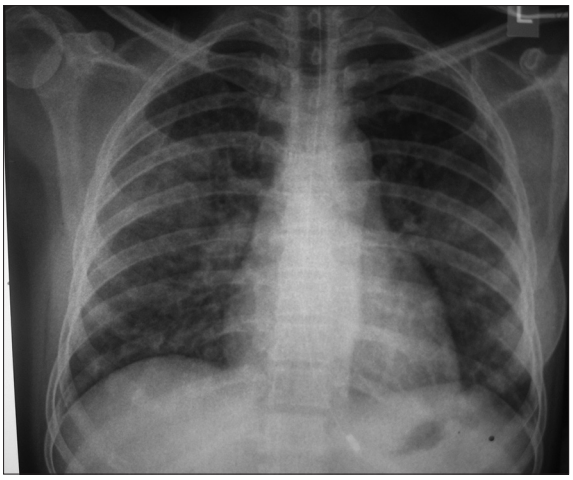

Figure 4: Chest radiography showed bilateral diffuse fluffy infiltrates (case 2)

Her laboratory investigations revealed TLC of 21,300 mm^3, hemoglobin of 7.8 gm/dl, and platelet count of 116,000 mm^3; AST, 373; ALT, 238; total bilirubin, 3.6 mg/dl; albumin, 1.7 gm/dl; total protein, 4 gm/dl; creatinine, 2.4 mg/dl; and urea, 84 mg/dl. CSF examination did not reveal any abnormality. Abdominal USG was normal. Her Weil-Felix test was positive for the OX-K antigen in titers of 1:320. Biopsy of eschar showed a lymphohistiocytic vasculitis, perivascular collections of lymphocytes with areas of ulceration, and necrosis of overlying epidermis. She was also started on chloramphenicol, but in spite of the intensive supportive care and antibiotic coverage, the patient succumbed to her illness on the 7th day of hospitalization due to multiorgan failure (MOF).

Discussion

In India, scrub typhus had occurred among troops during World War II in Assam and West Bengal, and in the 1965 Indo-Pak war. It has been reported from northern India (sub-Himalayan belt from Jammu to Nagaland, Himachal Pradesh), eastern India (Assam, West Bengal), and southern India (Tamil Nadu, Kerala).[1,5]

ARDS in scrub typhus is caused by direct or indirect lung injury related with rickettsial infection. Systemic vasculitis and perivasculitis as the main mechanism in the pathogenesis of scrub typhus was suggested by Strickman *et al.*[6] The authors proposed that vasculitis is caused by the proliferation of *O. tsutsugamushi* in endothelial cells of microvascular system leading to microangiopathies in major organs like heart, lung, brain, and kidney. Immunologic mechanism apart from vasculitis due to direct invasion of rickettsial organism is involved in the pathogenesis of pulmonary involvement of scrub typhus was suggested by Park *et al.*[7]

The diagnosis of scrub typhus is confirmed by serologic testing. The indirect immunofluorescence antibody test (IFA) remains the gold standard for serologic diagnosis. A four-fold rise in titers in paired samples drawn at least 14 days apart is conclusive. Other comparable alternatives available are the indirect immunoperoxidase (IIP) test, enzyme-linked immunosorbent assay (ELISA), passive hemagglutination assay (PHA), immunochromatographic assay (ICA), and immunoglobulin (Ig) M dot-immunobinding assay. Most of these tests are costly and not easily available in our country. Weil-Felix test is a useful and easily available tool when used and interpreted in the correct clinical context. The criterion for a positive result is either a four-fold rise in agglutinin titer in paired sera or a single high cut-off titer (≥ 1:320) at which the positive predictive value and the specificity is reliable.[8] A rapid ICA used in our study has been shown to be reliable and comparable to immunofluorescent antibody (IFA).[9] IFA test could not be done in our case due to its local nonavailability. The diagnosis in our both cases was based on presence of eschar, a positive Weil-Felix test, and a positive rapid diagnostic test for scrub typhus (ICA).

Scrub typhus is grossly underrecognized and neglected entity in various parts of India due to limited awareness and its nonspecific clinical presentation. To our knowledge, it has not been well-documented from Vidharba region of Maharashtra. We describe for the first time, cases of scrub typhus complicated with ARDS and MOF from Vidarbha region situated in central India.

Conclusion

Physicians or practitioners at primary care centers should carefully search for the presence of "eschar" (resembles cigarette burn mark surrounded by erythema) in a patient of acute febrile illness of unknown origin, which is an important clue in the diagnosis of scrub typhus. The eschar is often present in soft skin areas such as skin folds—axilla, groin, gluteal folds, breast folds, and external genitalia. Weil-Felix and immunochromatography tests may not come positive in the 1st week of illness and also not available at the primary healthcare level. Early recognition, clinical diagnosis, and treatment with doxycycline or tetracycline by the primary care physicians can prevent fatal complications of scrub typhus like ARDS, meningoencephalitis, shock, or

multiple organ dysfunction syndrome (MODS). Other antibiotics useful for the treatment of scrub typhus are chloramphenicol, azithromycin, and rifampicin.[10] A patient of scrub typhus with acute respiratory distress, altered sensorium, seizures, or ARF should be immediately referred to a tertiary hospital for early necessary intervention and intensive supportive care. Metabolic acidosis, ARDS, altered sensorium, and shock were observed as independent predictors of mortality in a study done by Chrispal *et al.*[11] Delay in diagnosis and treatment of scrub typhus result in increased mortality and morbidity. Primary care physicians must include scrub typhus as an important differential diagnosis in patients presenting with fever, cough, breathlessness, myalgia, headache, rashes, anorexia, vomiting, or abdominal pain and start empirical treatment with doxycycline early in the course of illness.

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