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A Case Series of Scrub Typhus from Eastern State of India

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ABSTRACT: Scrub typhus is one of the endemic diseases leading to acute febrile illness in the topical countries. It can present with its various manifestations ranging from asymptomatic illness to serious multiorgan dysfunctions. The most common pathophysiology behind this multisystem manifestation is the systemic vasculitis due to exaggerated immune response. Early diagnosis and aggressive treatment along with close monitoring of vitals with best supportive measures may be the satisfactory response to the physician. Here, in this case series we are discussing five cases of scrub typhus presented with various atypical and uncommon manifestation HLH (Case 1), Encephalopathy, Pancytopenia, AKI, Intrahepatic cholestasis, Pancreatitis (Case 2), meningoencephalitis (Case 3), myocarditis (Case 4) and Leukemoid reaction, ALF (Case 5).

KEYWORDS: Scrub typhus, Leukemoid reaction, meningoencephalitis, Intrahepatic cholestasis, Pancreatitis, myocarditis, Hemophagocytic Lymphohistiocytosis.

INTRODUCTION:

Scrub typhus is a mite borne infectious disease caused by orientia tsutsugamushi, a gram-negative intracellular bacterium. The reservoir and vector of the scrub typhus are larval trombiculid mite of the genus Leptotrombidium. It is transmitted to human beings by the bite of a larval mite (1). After hatching, infected larval mites inoculate organism into the skin. The disease was first described by the Chinese in the third century, but the first description of its classic features did not appear in the western literature until the end of nineteenth century (2). Scrub typhus is endemic and remerging in eastern and southern Asia, northern Australia and islands of the western pacific and Indian oceans. It is an endemic to a 13,000,000 km2 area of the Asia-Pacific rim, extending from Afghanistan to China, Korea, the islands of the southwestern Pacific, and northern Australia (3). Most of the cases present with fever, myalgia, rash, headache and sometimes manifests as serious organ damage with fatal complications like ARDS, myocarditis, meningoencephalitis, AKI etc. the pathognomonic finding in scrub typhus is a necrotic eschar, is rarely seen in south east Asia (4).

CASE SERIES:

CASE 1:

21year male without any comorbidity presented with high grade, intermittent fever for last 20 days, associated with chill and rigor. He had no history of pain abdomen, jaundice, hematemesis, melena, respiratory distress, cough or haemoptysis. He did not complaints of any dysuria, headache, vomiting, convulsion or skin rashes. On physical examination, he had mild pallor with mild hepatosplenomegaly and black eschar over left lower back **(Fig 1).** On evaluation, complete hemogram revealed pancytopenia ((Hb 9.3g/dl, TLC 1800 /mm3 , Platelet 55,000 /mm3) with raised inflammatory markers (CRP 30.67 mg/dl, LDH 1865 U/L, Ferritin 867mg/dl). Liver function test showed mildly elevated liver enzyme. He was evaluated for the fever due to common endemic infections. There was no evidence of malaria parasite on peripheral blood smear as well as Malaria Parasite Dual Antigen test was negative. Dengue IgM and Leptospira IgM were negative. He was sterile for blood and urine culture. **Scrub typhus IgM became reactive by ELISA method.**

He was put on intravenous doxycycline along with antipyretic. But, even after giving adequate dose of doxycycline; fever and pancytopenia were persisting. On subsequent evaluation, pancytopenia was progressive **(Hb - 7.3 g/dl, TLC 2800/mm3, Platelet 30,000 /mm3),** elevated liver enzyme **(AST 356 U/L, ALT 455 U/L)**, **hypertriglyceridemia (324 mg/dl), hyperferritinemia (>2000 mcg/L)** with hepatosplenomegaly on ultrasonography of abdomen. HLH was suspected and Bone Marrow Aspiration was

done which showed evidence of **Hemophagocytes (Fig 2).** He was diagnosed as HLH secondary to scrub typhus as per HS Score criteria. Other secondary causes of HLH have been ruled out. The patient was treated with pulse methylprednisolone1gm daily for 3 days with IVIG 1gm daily for 2 days and iv doxycycline for 14 days. He was improved dramatically both from clinical and biochemical point of view. His pancytopenia gradually resolved with liver enzymes and inflammatory markers were come down. He was discharged after complete recovery. So high index of suspicion and aggressive measures are needed to manage the peculiar and very rare complication of **Scrub Typhus associated Hemophagocytic Lymphohistiocytosis.**

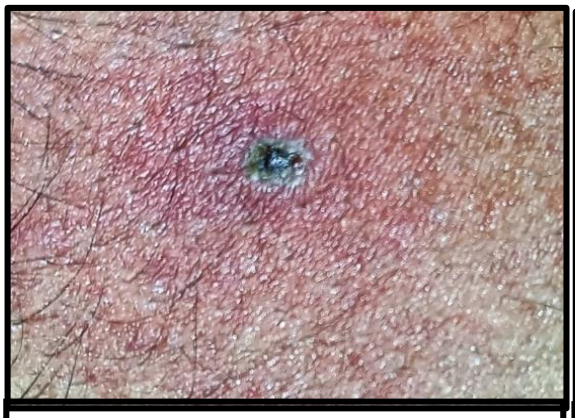

Fig 1: Black eschar over left forearm

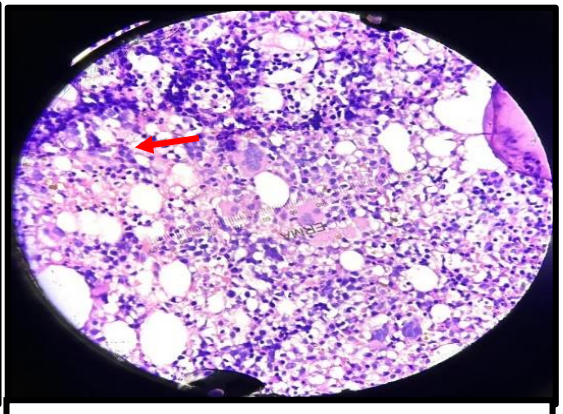

Fig 2: (Bone Marrow Biopsy): Shows hemophagocytes (red arrow)

CASE 2

28 years old male presented to the department of Medicine of our Institute with complaint of moderate grade intermittent fever for 10 days, yellowish discoloration of eye and urine for 7 days along with progressively decrease urine output for 5 days and altered sensorium for last 3 days. He had no history of headache, vomiting, convulsion, respiratory distress, chest pain and cough. There was no history of pain abdomen and skin rashes. Physical examination revealed GCS -10/15 (E3V3M4), bilateral pupils were sluggishly reactive, planter reflex bilaterally extensor. He had moderate pallor, icterus **(Fig -1),** with hypotension (BP 88/40 mmHg), tachycardia (PR-115/min) and tachypnoea (RR- 24/min). On GI System examination ascites was present with very sluggish peristalsis. Other systemic examinations were unremarkable. Complete hemogram revealed pancytopenia with Hb 8.8 gm/dl, TLC 3000/mm and platelet 90,000/mm3. LFT showed cholestatic hepatitis with elevated liver enzymes (Total bilirubin 10.2 mg/dl, direct bilirubin 6.4 mg/dl, SGPT 360 IU/L, SGOT 714 IU/L, GGT 481 IU/L). there was evidence of coagulopathy with PT 28.9 Seconds, INR 3.25 and APTT 38.9 Seconds. Serum ammonia was raised suggestive of hepatic encephalopathy. The kidney function also was deranged with urea 281mg/dl, creatinine 7.3 mg/dl, sodium 150 mEq/l, potassium 3.4mEq/l. Pancreatic enzymes were elevated with amylase 351mg/dl and lipase 478 mg/dl. All inflammatory markers were elevated (ESR 89mm, CRP 55.8 mg/dl, LDH 1045 U/L) but procalcitonin was negative. USG whole abdomen revealed hepatosplenomegaly, pancreatic head oedema, multiple dilated gut loops with sluggish peristalsis, mild ascites, raised cortical echogenicity with maintained corticomedullary differentiation of both kidneys. Serology for hepatotropic virus were negative. Endemic diseases like malaria, dengue, Leptospira were ruled out. Blood and urine culture were negative. Chest X Ray was normal. In the meantime, Scrub typhus IgM became reactive by the ELISA method. Initially he was treated symptomatically for acute liver failure, AKI and hypotension as well as pancreatitis. When scrub typhus became positive, the patient was treated with intravenous Doxycycline & azithromycin with other supportive measures like haemodialysis, TPN and others. Clinical and biochemical parameters of the patient gradually improved and he was discharged after complete recovery. In this way Scrub typhus can present multiorgan dysfunctions like Encephalopathy, Pancytopenia, AKI, Intrahepatic cholestasis and Pancreatitis.

Fig 1: Icterus of bilateral sclera

CASE 3:

35 years old male, known case of hypertension presented with complaints of moderate grade fever for 10 days, 2 episodes of convulsion and altered sensorium for last 3 days. He had no history of skin rash, bleeding manifestation, jaundice, pain abdomen or vomiting. On clinical examination, GCS was 7/15 (E2 V2 M3), bilateral pupil was very sluggishly reactive, plantar bilateral non responsive, all deep tendon reflexes were diminished, neck rigidity was present along with Kernig's sign was positive. He had BP- 146/92 mmHg, PR- 84/mins, SPO2- 93%, Chest- right sided coarse inspiratory crepitation. Other systemic examinations were unremarkable. Complete hemogram showed neutrophilic leucocytosis (Haemoglobin-11.5 gm/dl, TLC- 14,700/cmm, Platelet – 1.57 Lac). Renal function test revealed AKI (Urea- 227mg/dl, Creatinine- 2.3mg/dl). All inflammatory markers were raised (ESR- 75, CRP56.9mg/L, Ferritin- 899mcg/L). Chest Imaging (CXR and HRCT thorax) was suggestive of aspiration pneumonitis. As patient presented with acute encephalitis syndrome, MRI Brain was done which showed signal restriction in right parieto frontal & adjacent temporal region, possibility of meningoencephalitis **(Fig 1).** CSF study revealed lymphocytic predominance cells with high protein. CSF neuroviral panel was negative. There was no evidence of growth on CSF culture. EEG was done which showed encephalitis like changes. Common endemic disease like malaria, dengue and Leptospira were ruled out by doing specific serology. Blood culture revealed no growth. But scrub typhus IgM became reactive. He was treated with intravenous doxycycline & azithromycin, with other supportive measures. Patient was improved dramatically and all biochemical parameters were improved after 15 days of treatment.

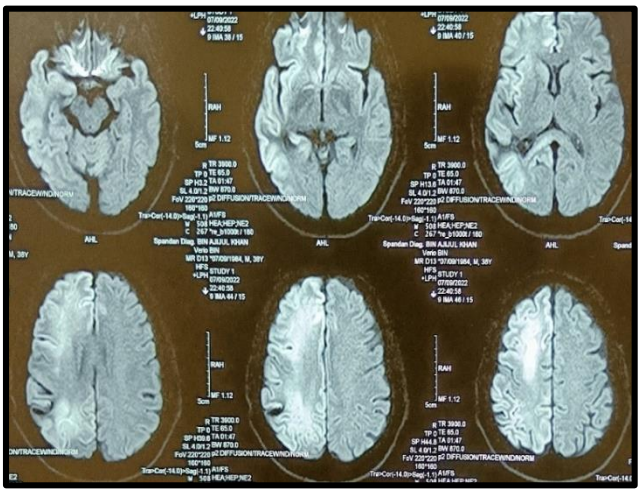

Fig 1: Signal restriction in right parieto frontal & adjacent temporal region

CASE 4:

52-year-old male presented to our department with complaint of intermittent high-grade fever for last 15 days, progressive oliguria for last 5 days and shortness of breath and chest pain for last 3 days. On physical examination, he had mild pallor, BP- 126/74, PR- 120, RR- 38/ mins, chest – B/L basal fine crepitation were present. A black eschar mark was present on left forearm **(Fig 1)**. On cardiovascular system examination there was LV S3 gallop. Urgent ECG was done which shows ST Segment elevation in lead V2, V3, V4, V5, V6, lead 1, AVL with ST Segment depression and T wave inversion in lead 2,3, AVF **(Fig 2).** 2D Echocardiogram showed global hypokinesia with ejection fraction of 41%, **features suggestive of myocarditis**. Complete hemogram revealed leucocytosis with mild anaemia (Hb 10.4gm/dl, TLC 15400/cmm, Platelet 1.53 lac), Renal function test showed AKI with urea 128 mg/dl, creatinine 7.1mg/dl. In liver function test, liver enzymes were mildly raised with bilirubin 1.9mg/dl, direct 1.6mg/dl, ALT 68 U/L, AST 141U/L, cardiac enzymes were elevated with CPK MB 47 IU/L and Trop I 541ng/ml. Patient was managed with intravenous diuretics with Intravenous Doxycycline empirically for the lifesaving purpose. In the meantime, Scrub typhus IgM antibody became reactive. Patient was regularly monitored with clinical and biochemical parameters, which gradually improved. Heart failure and AKI were gradually resolved. Patient was discharged after complete recovery at hemodynamically stable condition.

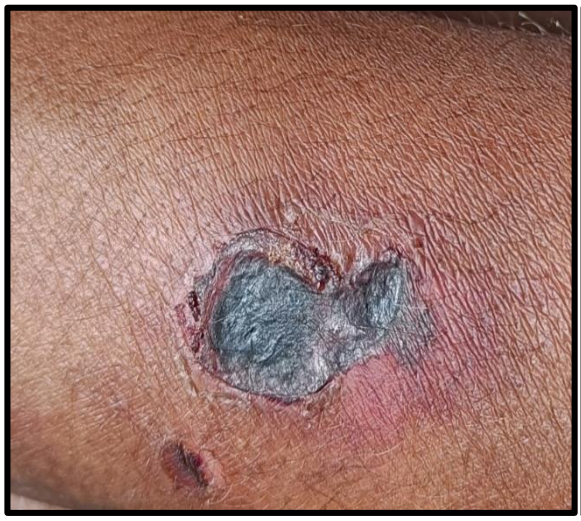

Fig 1: Black eschar mark on left forearm

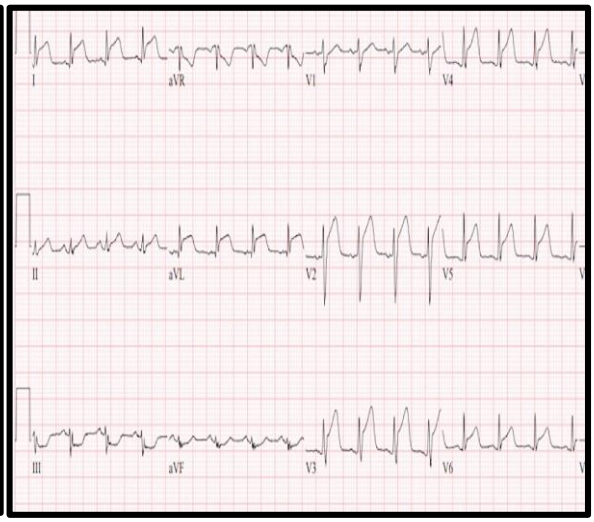

Fig 2: ST segment elevation lead V2, V3, V4, V5, V6, lead 1, AVL (red arrow) with ST Segment depression and T wave inversion in lead 2,3, AVF

CASE 5:

A 40 years old female from rural area of India, without any known comorbidity presented with fever for 14 days, jaundice for 5 days, altered sensorium & chest for 2 days. Fever was high grade, intermittent, associated with chill and rigor. The jaundice was gradually progressive. The chest pain was diffuse, dull aching and non-radiating. She became disoriented 2 days prior to admission. There was no history of pain abdomen, vomiting, skin rash, oral ulcer, cough, shortness of breath, hematemesis, Malena, headache and convulsion. On physical examination, GCS was 9/15 (E2V3M4), pulse rate 120/min, blood pressure 106/68 mmHg, respiratory rate 24/min with no skin rashes. She had mild pallor with icterus. There was diffuse tenderness over right hypochondrium on gastrointestinal system examination. She had bilateral plantar extensor. S3 gallop with bilateral basal fine crepitation was present cardiovascular system examination. Complete hemogram revealed anemia, marked leukocytosis with thrombocytopenia (Hb 8.8 gm/dl, TLC 88,440/cmm, Platelet 90,000/cmm) and left shift on peripheral blood smear. Liver function test showed conjugated hyperbilirubinemia with markedly elevated liver enzyme (total bilirubin 8.4 mg/dl, direct/indirect 5.2/ 3.2, AST 3300 U/L, ALT 3984 U/L) which was suggestive of **acute hepatitis**. There was coagulopathy with PT 22.4 Seconds, INR 4.52 and APTT 33.8 seconds. Serum ammonia was raised (98.6 mcg/dl) which correlate with hepatic encephalopathy. All the inflammatory markers were raised (CRP 45.7mg/dl, ESR 88mm, LDH 866 U/L, Ferritin 945 mcg/L) but procalcitonin was negative (0.4 ng/ml). Ultrasonography of abdomen showed features of acute hepatitis. Chest x-ray was suggestive of plethoric lung field with perihilar congestion. There was no evidence of any microorganism in blood and urine culture.

Serology for hepatotropic virus (hepatitis A, B, C and E virus), dengue IgM and IgM Leptospira were negative. There was no evidence of malaria parasite in peripheral smear as well as MPDA (Malaria Parasite Dual Antigen) test were negative. She was positive for scrub typhus IgM detected by ELISA method.

For chest pain, ECG was done, showing ST segment depression on lead V5, V6, lead 1 and aVL) with elevated CPK MB and troponin I , global hypokinesia and 44% ejection fraction on 2D Echocardiography which was suggestive of myocarditis.

For leukocytosis, bone marrow study was done which showed reactive marrow. For reactive marrow with leukocytosis, LAP Score was done which was very high, suggestive of leukemoid reaction.

Initially she was treated symptomatically for acute liver failure and myocarditis. After scrub typhus report became positive, she was treated with intravenous doxycycline for 14 days. The patient was symptomatically improved with normalization of liver enzyme, leukocyte count, cardiac enzyme as well as ST-T changes on ECG.

DISUSSION

The common clinical features of scrub typhus are fever with chills, rashes, and non-specific symptoms like headache, myalgia, sweating, and vomiting (5). Patients may manifest gastrointestinal (hepatitis, splenomegaly), respiratory (pneumonia, ARDS), neurological (meningoencephalitis), or ocular (conjunctival injection, subconjunctival haemorrhage) symptoms (6). The clinical features may also resemble other tropical infections like enteric fever, malaria, dengue, or leptospirosis (6). But eschar is a

characteristic finding in about half the patients with proven scrub typhus (6). Previous literature has reported the presence of eschar in 43.5-87% of the cases from different studies (6,7,8). It is pathognomonic of scrub typhus (9) but is often unreported by patients as it is painless and non-pruritic (10). A meticulous physical examination to search for eschar often helps to make a diagnosis of scrub typhus, so that treatment can be initiated early HLH is potentially serious consequences of scrub typhus. Hemophagocytic Lymphohistiocytosis is an aggressive and life-threatening condition with excessive immune system activation resulting in hypercytokinemia and multiorgan failure (11). Many patients with HLH have a predisposing genetic defect and or immunological trigger which may be infection, malignancy, connective tissue disease or disorder associated with immune dysregulation (12). In our case **(Case 1),** it was due to scrub typhus. There are only few case reports showing scrub typhus as a trigger of HLH. Scrub typhus with hemophagocytic syndrome can result in DIC and multiorgan failure. Despite its rarity, scrub typhus may be lethal; as a result, practitioners must be aware of the necessity of detecting and treating suspected cases as soon as possible. Gastrointestinal manifestations are not uncommon in scrub typhus, such as nausea, vomiting, diarrhoea and hematemesis or melena being reported. (13). pancreatitis is a very rare complication of scrub typhus. The mechanism of pancreatitis in infective conditions is postulated to be due to bacterial translocation (14), However, in the case of scrub typhus the mechanism of pancreatic involvement remains unclear; although, it is theorized that vasculitis may be the cause (15). Antibiotic therapy for the scrub typhus along with supportive therapy for pancreatitis, can result in a good outcome for the patient **(Case 2).** Abnormal liver function is well documented in scrub typhus (16), but cholestatic hepatitis is rarely reported. In our patient **(Case 2),** cholestatic hepatitis was diagnosed on basis of conjugated hyperbilirubinemia and high ALP, GGT level, that was improved after doxycycline therapy. Pancytopenia is a rare complication in scrub typhus and is often related to hemophagocytosis (17). In our case **(Case 2),** Pancytopenia was resolved after doxycycline therapy and it was not related to HLH. AKI in scrub typhus is usually mild and non-oliguric (18). In our patient **(Case 2),** Complete renal recovery occurred after doxycycline therapy. Patient presents with acute febrile illness with AKI, Scrub typhus should be part of the differential diagnosis. Scrub typhus meningoencephalitis is a common complication of scrub typhus. Most of the patient present as acute febrile illness with altered sensorium and meningeal sign. CSF analysis shows mild to moderate rise in protein with low to normal glucose (19). CSF Lymphocytic pleocytosis may be helpful in differentiating it from bacterial meningitis, but tubercular meningitis remains a close differential diagnosis (20). Thus, a high degree of clinical suspicion and a positive rapid, diagnostic test remains an important point in the management of scrub typhus as the timely initiation of specific therapy results in complete recovery and fewer complications. In our case **(Case 3),** the patient was diagnosed scrub typhus meningoencephalitis and completely recovered with doxycycline therapy. Myocarditis rarely reported, postulated to be caused by localized infection in endothelial cells of heart and cardiac myocytes (21). Scrub typhus myocarditis can be a subclinical manifestation of cardiac involvement, some patients with scrub typhus might have undetected mild myocarditis. In our case **(Case 4),** the patient presented with chest pain with tachycardia and s3 gallop suggested myocarditis, which was confirmed by ECG findings, elevated cardiac enzymes and 2D echocardiography. Elevation of liver enzymes is common in scrub typhus but acute liver failure is rarely reported in literature (22). In our patient **(Case 5),** the patient was diagnosed ALF due to scrub typhus based on the presence of marked elevation of hepatic transaminases, coagulopathy and encephalopathy, after ruled out viral hepatitis (HBV, HCV, HAV and HEV) and that was completely responded with doxycycline therapy. Leukemoid reaction which, is very unusual following scrub typhus, can be explained as physiological response to overwhelming infection, which releases stimulatory molecules like growth factors (G-CSF, GM-CSF, C-KIT ligand), adhesion molecules (CD11b/CD18) and various cytokines (IL-1, 3, 6, 8, TNF) (23). It often mimics haematological malignancy and could be differentiated by elevated LAP score (24,25). In our case **(Case 5),** leukemoid reaction was diagnosed for leucocytosis by LAP score after ruled out haematological malignancy. The leucocytosis was gradually normalized after doxycycline therapy for scrub typhus.

CONCLUSION

In a tropical country like India, scrub typhus serology should be done in acute febrile patient presenting with HLH (Case 1), Encephalopathy, Pancytopenia, AKI, Cholestatic Hepatitis, Pancreatitis (Case 2), meningoencephalitis (Case 3), myocarditis (Case 4) and, ALF and Leukemoid reaction (Case 5).Scrub typhus infection has an excellent therapeutic response to inexpensive antibiotic like doxycycline, Early therapeutic intervention with doxycycline should be intensified in endemic countries like India. Scrub typhus has emerged as a common aetiology of febrile illness in south east Asian countries like India. It is underrecognized infection, which may present with serious multiorgan complications like HLH, meningoencephalitis, Pancytopenia, AKI, Cholestatic Hepatitis, Pancreatitis, myocarditis and acute liver failure. Leukemoid reaction may be seen in scrub typhus like other triggering infections. In patients with acute febrile illness with HLH, meningoencephalitis, Pancytopenia, AKI, Cholestatic Hepatitis, Pancreatitis, myocarditis and acute liver failure and /or myocarditis, scrub typhus should be ruled out in all cases. Timely diagnosis of disease and initiation of therapy with doxycycline/or azithromycin leads to excellent prognosis.

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CONSENT: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

GUARANTOR: Prof. Dr. Soumitra Ghosh

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