Case Report

Scrub typhus, a rare of cause of fulminant hepatic failure: A common disease with uncommon presentation

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ABSTRACT

Scrub typhus (bush typhus) is a potentially lethal mite-borne, acute febrile infectious illness caused by *Orientia tsutsugamushi*, reported precipitating frequent outbreaks in the Asia-pacific belt. Usual presentation after a median incubation period of 10–14 days, stretches from pathognomonic eschar, high-grade fever, centrifugal skin rash, jaundice, regional lymphadenopathy to frontal headache, nevertheless complicated at times with myocarditis, acute respiratory distress syndrome, acute kidney injury, encephalitis, and shock. Although patients with scrub typhus invariably do display mild liver injury, fulminant hepatic failure (FHF) is rarely reported. We describe herein, a case of FHF in an elderly male that responded well to antibiotics. Early diagnosis and sensitive antibiotic administration aids in mortality prevention of the former.

Keywords: Doxycycline, Fulminant hepatic failure, Scrub typhus, South-Asia

Among Rickettsial infections, scrub typhus is relatively endemic and found in ease in the out-patient settings, with undifferentiable symptoms from other tropical infections. For this, it needs close attention for its expected life-threatening complications aforesaid more common in the 1st week of illness [1,2]. The liver injury usually manifests as elevated hepatic enzymes and bilirubin, which usually reverses on appropriate and prompt treatment initiation [2].

We report the case of an elderly male with no medical comorbidities, who presented with fever, jaundice, and later progressed to frank encephalopathy secondary to scrub typhus infection. With adequate antibiotics and auxiliary care, he eventually improved completely and was discharged after 7 days of admission.

CASE REPORT

A 60-year-old elderly male with no identified medical comorbidities, presented to the medical emergency room of our hospital on December 30, 2020, with complaints of high-grade documented fever with chills, persistent vomiting, yellowish discoloration of eyes, mild diffuse upper abdominal pain, and non-productive cough for 5 days followed by altered sensorium for the last 2 days then. History of occasional alcohol intake for 2 years was present with no other recreational drug intake in the past. No history of similar illness or jaundice in the past nor any prior hospitalization. History of anti-tubercular treatment intake for 6 months for sputum-positive pulmonary tuberculosis before 6 years was recorded.

On preliminary examination, he was ill-looking, somnolescent, drowsy, and not responding to oral commands, with a Glasgow coma scale of 9/15. Physical examination revealed pallor, deep icterus, and a macular erythematous rash all over the trunk. No evident black eschar or regional lymphadenopathy was found. The vitals at the time of admission, namely, an axillary temperature of 102°F, blood pressure of 94/66 mmHg, respiratory rate of 14/min; abdomino-thoracic type, and a regular pulse of 106/min were recorded. Oxygen saturation by pulse oximetry was 96% in room air and random blood glucose was 86 mg/dl. Per abdominal examination revealed tender hepatomegaly palpable about 3 cm below the right costal margin in the midclavicular line. The edges were smooth and no nodularity felt over the liver. The bowel sounds were audible, with no other organomegaly or evidence of free fluid in the abdomen. The respiratory and cardiovascular examination was unremarkable except for tachycardia. Pupils were 3 mm and reacting to light. No signs of meningism were present.

The initial blood investigations are shown in Table 1. Arterial blood gas revealed a partially compensated metabolic alkalosis with a pH of 7.55.

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Table 1: Serial blood investigation of the patient

Name of the test	Day 1	Day 2	Day 3	Day 5	Day 6
Hemoglobin (g/dL)	10.6	8.9	9.2	8.3	8.8
Total leukocyte count (count/mm^3)	24,200	22,100	18,600	15,800	10,400
Differential count	$N_{84}L_{07}E_{04}$	–	–	–	–
Platelet count (count/mm^3)	95,000	62,000	77,000	89,000	1,55,000
Serum sodium (mEq/L)	138	136	133	131	136
Serum potassium (mEq/L)	3.1	2.6	3.6	4.2	4.1
Total bilirubin (mg/dL)	10.6	11.9	8.9	6.4	5.5
Direct bilirubin (mg/dL)	5.7	6.9	4.4	3.9	3.1
Aspartate amino transferase (U/L)	262	111	71	88	35
Alanine amino transferase (U/L)	298	106	69	62	41
ALP (U/L)	981	367	350	266	280
Blood urea (mg/dL)	85	111	52	41	24
Serum creatinine (mg/dL)	1.6	1.1	1.1	0.6	0.6
Prothrombin time	–	56.2	31.4	20.1	12.7
Partial thromboplastin time	–	40.9	32.7	31.5	28.6
INR	–	5.08	3.11	1.74	1.0

***SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio**

Chest radiography was unremarkable. An electrocardiograph revealed sinus tachycardia and global T-wave inversion (secondary to severe hyperkalemia). Immediate potassium correction was done stat after a preliminary report of 2.6 mEq/L. Screening ultrasound examination of the abdomen revealed hepatomegaly with raised echotexture and a normal portal vein Doppler study (Fig. 1). Cholelithiasis (6 mm) was present but the biliary tree (common bile duct) and intrahepatic biliary radicles were not dilated. Screening non-contrast computed tomography of the brain and cerebrospinal fluid (CSF) analysis unveiled no significant abnormality. Along with basic blood investigations (Table 1), depending on the regional prevalence, serologies for malaria (Rapid antigen card), leptospira, typhi-DoT, scrub typhus, dengue, chikungunya, and hepato-trophic viruses were sought. Early morning mid-stream urine for cytology, microscopic examination (of the active sediments/casts) and bacterial culture were sent.

In addition to supportive care (including laxatives in suspicion of hepatic encephalopathy) and parenteral hydration, he was started empirically on intravenous artesunate (for severe malaria), Ceftriaxone (for uncomplicated urinary tract infections/ leptospirosis), and Doxycycline (for Scrub typhus). Lactulose enema was administered given constipation and suspected hepatic encephalopathy. Peripheral blood smear showed macrocytic anemia with hyper-segmented neutrophils and did not reveal any malarial parasite.

Samples for serum ammonia and cobalamine/folate levels/ reticulocyte count/serum lactate dehydrogenase (LDH) were sent. On day 2 of admission, serologies of all aforesaid tropical infection and hepato-trophic viruses (Hepatitis A, B, C, and E) came out negative except for Scrub typhus immunoglobulin antibody for *Orientia tsutsugamushi* (By enzyme-linked immuno-sorbent assay). The diagnosis of scrub typhus was further confirmed by real-time polymerase chain reaction. Quantitative C-reactive protein was negative. The blood and urine cultures were sterile. The antibiotics were modified accordingly (Ceftriaxone and artesunate were stopped and Doxycycline was continued) on the next day. Serum ammonia level was 380 µmol/L and cobalamin was 111 pg/mL. Fibro scan of the liver showed coarse echogenicity, an average kPa was 9 and average velocity measure being 1.8 m/s. Corrected reticulocyte count was 0.34% and LDH was 742 U/L. Intravenous B12 supplementation was started on day 4.

Despite coagulopathy (International normalized ratio – 5.08), the patient did not develop any bleeding manifestation during the hospital stay. A final working diagnosis of scrub typhus infection complicating fulminant hepatic failure (FHF) with megaloblastic anemia was made. His sensorium and lab parameters gradually improved and he became afebrile from day 4. With conservative management, he was discharged with oral medications and supplements on day 7. In follow-up after 6 weeks, his serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and total serum bilirubin levels were 34 U/L, 53 U/L, and 1.5 mg/dL, respectively, and his liver was not palpable clinically then.

DISCUSSION

Scrub typhus in the 21st century has become endemic in third world countries especially the "tsutsugamushi triangle" of the Asia-pacific region [1-3]. As previously noted, it is a potentially lethal febrile illness transmitted by the bite of larvae of trombiculid mites. In usual circumstances, the illness goes uncomplicated, but complications, which can even be fatal, commonly occur in untreated patients. After an incubation period of 1–3 weeks, it usually presents with an array of symptoms, namely, typical black eschar at the bite site following high-grade fever with chills, myalgia, headache, cough, generalized lymphadenopathy,

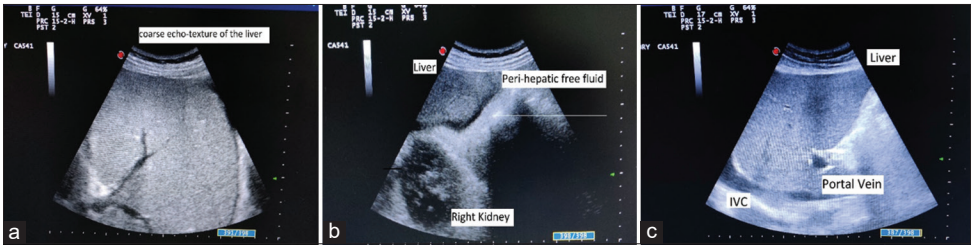

Figure 1: (a) Ultrasound images (a) showing altered echotexture of the liver; (b) of the abdomen right upper quadrant; (c) of the inferior surface of the liver with inferior vena cava

jaundice, and gastrointestinal symptoms. The pathogenesis of the disease process is thought to cause disseminated vasculitic and peri-vascular inflammation, landing in significant plasma leakage and end-organ damage multiple organ dysfunction syndrome [2,4].

Hepatic injury is frequently of mild acute hepatitis with nominal enzyme elevation, hyperbilirubinemia, coagulopathy, and rarely FHF [5]. Our patient had presented with hepatic encephalopathy Grade 3 (normal CSF studies and neuro-imaging) with coagulopathy fulfilling the diagnosis of FHF (West Haven criteria) [6]. Subtle fibrosis (reasonably normal [F2 grade] fibro-scan of the liver) and normal portal venous Doppler stands against any previous hepatic illness. He also likely had pre-renal azotemia that improved after adequate parenteral hydration and critical care.

There are only a few case reports in the knowledge of the authors, with scrub typhus infection ensuing in hepatic failure, especially a pregnant female from Chandigarh, India who eventually succumbed to the illness [7]. One case report from the Himalayan state of Uttarakhand, India presented analogous to the index case, bolstered up after timely conservative management. In a retrospective short report by Hu *et al*. [5], from Taiwan, 90% of the patients had a significant surge in SGOT, SGPT, and gamma-glutamyl transferase although alkaline phosphatase was found to be raised in 35–40% of the participants. In agreement with our diagnosis, Shioi *et al*. [8] reported an autopsy of a scrub typhus patient who drowned in virtue of acute liver failure. Not surprisingly, findings were of submassive hepatic necrosis, infiltrates in the Glisson's capsule, and sporadic fibrin thrombi in the sinusoids backing disseminated intravascular coagulation. Countable reports [9-11] on pediatric cases of FHF with scrub typhus or coinfection with acute hepatitis A are encountered in the English literature. Prevention of clinical deterioration and demise is quite effortless, provided the early diagnosis and appropriate treatment initiation.

CONCLUSION

The minimal hepatic injury along with multi-organ dysfunction is not uncommon with scrub typhus infection, incidence of FHF is scarce. Vigilant screening and triage of patients with febrile illness in the outpatient department of any overburdened tertiary care facility in tropical countries may ease early diagnosis and mitigation of any complications. Hepatic derangements should be closely monitored with justified hospital admission to avoid FHF, though rare in common clinical settings.

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