Hepatitis E Virus Induced Acute Liver Failure with Scrub Typhus Coinfection in a Pregnant Woman

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Coinfections contribute significantly to diagnostic challenges of acute febrile illnesses, especially in endemic areas. The confusion caused by overlapping clinical features impedes timely management. Herein, we report an unusual, previously unreported case of a pregnant woman suffering from a coinfection of scrub typhus and hepatitis E virus. A 25-year-old, 31-week pregnant woman presented with jaundice for 5 days and altered sensorium for 2 days. She had features of both viral acute liver failure (ALF) and tropical infections mimicking ALF, including hyperbilirubinemia, coagulopathy, anemia, thrombocytopenia, intravascular hemolysis, and hepatosplenomegaly. Etiological workup revealed rare coinfection of hepatitis E and scrub typhus. Despite all supportive measures, the patient succumbed to her illness (i.e., absent brainstem reflexes and intracranial bleed secondary to coagulopathy) and had poor fetal outcome, which resulted in stillbirth. ALF in a pregnant woman is a medical and obstetric emergency. It can result from varied etiologies that though differ in their incidence, mode of occurrence, and pregnancy outcome, can clinically masquerade as each other, causing diagnostic dilemma. This unusual case report highlights the significance of keeping all such possibilities in mind while managing a pregnant woman with ALF, especially in a country like India where maternal and perinatal mortality rates, the core indicators of national health, are still among the highest in the world. (J CLIN EXP HEPATOL 2017;7:158–160)

Coinfections contribute significantly to diagnostic challenges of acute febrile illnesses, especially in endemic areas. The confusion caused by overlapping clinical features impedes timely management. Herein, we report an unusual case of a pregnant woman suffering from a coinfection of scrub typhus and hepatitis E virus (HEV).

Scrub typhus is an acute febrile illness caused by a rickettsial organism *Orientia tsutsugamushi*, which is transmitted to humans by the bite of the larva of trombiculid mites (chiggers). India, especially the sub-Himalayan zone,¹ is endemic for it. Although pregnant women may have similar clinical manifestations as the nonpregnant ones, there is an increased risk of fetal loss and preterm delivery if scrub typhus is acquired during pregnancy.²

Another infectious disease highly endemic in the Indian subcontinent is acute viral hepatitis, with HEV contributing to acute liver failure (ALF) and high mortality in pregnant women.³

Scrub typhus and HEV, although distinct in their mode of transmission, have several overlapping manifestations like prodromal phase, fever, jaundice, hepatic involvement, progression to encephalopathy, etc. The simultaneous occurrence of both these infections in the same patient, although not reported in literature before, is a possibility and may cause inadvertent delay in the initiation of appropriate treatment.

CASE REPORT

A 25-year-old, 31-week pregnant woman hailing from sub-Himalayan region presented with jaundice for 5 days and altered sensorium for 2 days, preceded by prodrome: fever, malaise, anorexia, and vomiting for 3 days. On examination, she had tachycardia pulse rate of 110/min and BP of 106/64 mm of Hg. She had fever, icterus, and pedal edema. She was disoriented with Glasgow scale E2V1M4 and had no focal neurological deficit. Investigations revealed anemia (Hb 8.6 g/dl), thrombocytopenia (43,000/ μ L), and normal Leukocyte count (6200/ μ L); peripheral blood film showed dimorphic anemia and 1% schistocytes. Raised plasma hemoglobin (44 mg/dl) and LDH (656 U/L) suggested hemolysis. She had conjugated hyperbilirubinemia (total/direct: 10.9/8.7 mg/dl), elevated liver enzymes (AST/ALT: 920/748 U/L, SAP: 200 U/L), deranged coagulogram (INR: 3.43), and normal renal functions (serum creatinine: 0.9 mg/dl). Ultrasound abdomen showed hepatosplenomegaly and single, live intrauterine fetus.

The etiological workup for ALF was positive for hepatitis E, anti-HEV IgM (OD = 3.9; cut-off >0.2, DiaPro, Milan,

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Abbreviations: ALF: acute liver failure; ALT: alanine transaminase; AST: aspartate transaminase; HAV: hepatitis A virus; HBV: hepatitis B virus; HEV: hepatitis E virus; LDH: Lactate dehydrogenase

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Italy). In view of ongoing fever and thrombocytopenia work up for common tropical infections mimicking viral hepatitis was done. The antibodies for *O. tsutsugamushi* IgM (OD = 0.644; cut-off >0.468, InBios International Inc., Seattle, WA, USA) turned out to be positive, and scrub typhus was confirmed by nested PCR targeting nucleotide sequences for gene encoding the 56 kDa antigen of Gilliam strain of *O. tsutsugamushi*.⁴ The PCR product was sequenced and registered in the GenBank (accession number KU500414). Viral markers for HAV, HBV, HCV, and tropical infections like dengue, malaria (peripheral blood smear, QDxMP card test), typhoid fever (Widal, blood culture), and leptospirosis (IgM ELISA) were negative.

She was managed as ALF as per protocol, prophylactically intubated for grade III hepatic encephalopathy, and started on antihepatic coma regimen, N-acetyl cysteine infusion, bolus iv mannitol to prevent surges of raised ICT, iv fluids, and other supportive measures. Empirically, the patient received injection ceftriaxone, and azithromycin was added once the scrub typhus serology came positive. Over the next 24 h, sensorium of the patient deteriorated to E1V1M1 with absent brainstem reflexes; CT scan head revealed large left frontotemporoparietal subdural hemorrhage with midline shift. Neurosurgery consultation was sought; however, in view of extensive intracranial bleed and absent brain stem reflexes, she was continued on supportive measures only. She delivered a stillborn baby on day 3 of hospitalization. In view of the grave prognosis, the relatives refused for further treatment and took voluntary discharge. A final diagnosis of concurrent infection of HEV with scrub typhus, manifesting as ALF along with multiorgan dysfunction, was made.

DISCUSSION

The majority of cases of ALF in India result from acute viral hepatitis (HBV/HEV/HAV). However, certain tropical infections like falciparum malaria, leptospirosis, dengue fever, rickettsial, and typhoid fever can present with altered sensorium and/or bleeding manifestations in presence of jaundice and mimic ALF. There are subtle differences to differentiate ALF due to viral causes from ALF mimickers. In retrospective analysis,⁵ certain variables associated with viral ALF were presence of grade III–IV encephalopathy, INR >2, ALT and AST >5 × ULN or >10 × ULN, hypoglycemia, normal hemoglobin (>12 g%), leukocyte (4000–11,000 cells/cumm), and platelet (150,000–500,000 cells/mm³) count. Those with infections mimicking ALF had high-grade fever (>102 °F), splenomegaly, ALT or AST <5 times upper limit of normal value (ULN), higher AST or LDH than ALT, and INR <1.5 (normal PT). Herein, we describe a case that had clinical features of both viral and infectious diseases mimicking ALF. The presence of prodrome, cerebral edema, AST/ALT elevation up to 20 times, INR >2.0, and raised arterial ammonia favored viral ALF.

However, ongoing fever, presence of hepatosplenomegaly, thrombocytopenia, and hemolysis favored ALF mimickers.

Coinfections of HAV/HEV with leptospirosis, malaria, and dengue are well reported in literature and are not so uncommon, especially in endemic countries. Coinfections with scrub typhus and leptospirosis have also been reported from the endemic ‘*tsutsugamushi* triangle’ belt.⁶ Scrub typhus concomitantly infecting patient of Hantavirus has been reported from China,⁷ but a coinfection of scrub typhus with other viral diseases has not yet been reported in world literature. In a study from India, HEV coinfection was found in 13 cases of leptospirosis and one case of dengue, with one rare case of triple infection with HEV, dengue, and malaria.⁸ Data regarding coinfection specifically in pregnancy is limited to a single study by McGready et al. describing coinfection of scrub typhus with malaria and dengue among pregnant women of Thai-Burmese border region.⁹

The coinfection of HEV with scrub typhus has not been reported earlier. In our patient, serology confirmed the presence of HEV and *O. tsutsugamushi* coinfection preterminally, which was later confirmed by PCR and sequencing. IgM ELISA for HEV with high positive predictive value (sensitivity = 5 IU/ml; specificity = 100%) was a strong indicator toward HEV-induced ALF in our patient.

Pregnant women are not only infected with HEV at an increased frequency than general population (12–20% vs 2–4%) but are also at higher risk of mortality (10–39% vs 0.06–12%).¹⁰ The rate of fetal loss can be as high as 42.6%.³ Our patient had stillbirth during the hospital stay. The coexisting multiple etiologies most likely contributed to the rapid deterioration culminating in an unfavorable outcome in our patient.

CONCLUSION

ALF in a pregnant woman is a medical and obstetric emergency. It can result from varied etiologies that though differ in their incidence, mode of occurrence, and pregnancy outcome, can clinically masquerade as each other, causing diagnostic dilemma. This unusual case report undermines the significance of keeping all such possibilities in mind while managing a pregnant woman with ALF, especially in a country like India where maternal and perinatal mortality rates, the core indicators of national health, are still among the highest in the world.

CONFLICTS OF INTEREST

The authors have none to declare.

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