Case report of atypical scrub typhus in pregnancy coexistent with HELLP syndrome mimicking pregnancy specific liver disease (P-sLD): A management dilemma

Sasirekha Rengaraj, Veena Ranjan, Shree Bharati, Kirti Girish Deodhare, Sanghamitra Hazarika

ABSTRACT

Introduction: Jaundice is one of the most dreaded medical disorders in pregnancy. Infective causes of jaundice are often confused with pregnancy specific liver disorders (P-sLD) like HELLP syndrome and acute fatty liver of pregnancy. Delivery may be needed in some situations irrespective of the etiology.

Case Report: We report a case of preeclampsia (PE) complicated by HELLP syndrome which mimicked thrombotic microangiopathy (TMA) in the postpartum period coexistent with atypical scrub typhus. The diagnostic dilemma at presentation, the challenges surrounding its management, and the recovery following antibiotic treatment with doxycycline are described with a review of the literature.

Conclusion: Infective causes of jaundice in endemic areas cannot be ignored even in straightforward cases of HELLP syndrome especially when it presents as P-sLD.

Keywords: AFLP, HELLP syndrome, Jaundice, P-sLD, Scrub typhus

INTRODUCTION

Jaundice in pregnancy is an alarming medical condition with an unpredictable course. Conditions such as acute fatty liver of pregnancy (AFLP) and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome which may be associated with jaundice often lead to adverse maternal and perinatal outcomes [1, 2]. Although prompt delivery is the appropriate management in both the conditions, preparing for delivery in the setting of coagulopathy is challenging [3]. The clinical distinction between these two conditions may not always be possible at the time of initial presentation however some salient features specific to both conditions help us to make a clinical diagnosis toward the end. During this Covid-19 pandemic, we faced a critical situation where possible HELLP/AFLP was complicated with co-existent
CASE REPORT

A 26-year-old G2P1L1, homemaker from rural area, was referred from a district hospital at 27+4 weeks of gestation with complaints of pain in abdomen and high blood pressure (BP) recordings of 170/100 mmHg for which she was given oral labetalol and loading dose of intravenous Magnesium Sulfate (MgSO4). There was no history of fever, pruritus, blurring of vision, reduced urine output, or vaginal bleeding. A detailed family history revealed that the first child was diagnosed to have nephrotic syndrome at the age of 3 and is currently under remission on a minimal dose of steroid. There was no other significant past or family history. She was perceiving fetal movements well. She was conscious and coherent at the time of admission. General examination revealed mild pallor, grade II pedal edema, conjunctival chemosis, and deeply icteric and there was no cyanosis. She was afibrile at the time of examination. There was mild facial puffiness. Her vital signs revealed a pulse rate (PR) of 66/min which was regular in rhythm, BP of 160/110 mmHg, respiratory rate (RR) of 18/min. Deep tendon reflexes were exaggerated at the time of admission. Examination of the cardiovascular, respiratory, and neurological systems did not reveal any abnormalities. There was moderate hepatomegaly which was non-tender. There was no splenomegaly or generalized lymphadenopathy.

Her obstetric examination revealed an enlarged uterus consistent with 24 weeks gravid uterus size and was relaxed and non-tender. Fetal parts were felt on examination and fetal heart sounds were well heard with Doppler. Speculum examination was normal, there was no bleeding and the cervical findings did not show any signs of labor. Bedside urine examination showed 4+ proteinuria. As the PR was <70/min, oral nifedipine was started as an antihypertensive and MgSO4 was continued. Obstetric ultrasound showed a singleton live fetus of 14th centile growth with normal liquor and there was no evidence of abortion. Her laboratory parameters are given in Table 1. As there was an increase in serum bilirubin and liver enzymes with raised lactate dehydrogenase (LDH) values and normal platelet count, the working diagnosis was either severe PE/HELLP or AFLP. Her Swansea criteria score was 5 at the time of initial presentation. Her renal parameters were normal at admission, and output was adequate. The high risk was explained to the family members and a joint decision was taken for termination of pregnancy. Blood products were arranged. Pregnancy was terminated with a combination of the mechanical and pharmacological methods [Extra-amniotic saline infusion (EASI) and 2 doses of 200 mcg prostaglandin E1] and she delivered an alive female baby of 730 g with 5 minute Apgar of 6 within 12 hours of labor induction. The baby was shifted to neonatal intensive care unit (NICU) level III and succumbed on post-natal day 3 due to prematurity and sepsis. Subsequently, on post-natal day 1, there was a gradual worsening in the renal function with development of an anuria and later in another few days liver function too deteriorated slowly following delivery. The absence of coagulopathy and hypoglycemia (though occur in a minority of patients, refractory hypoglycemia points toward AFLP) during the hospital stay ruled out the possibility of AFLP. The peripheral smear showed normocytic normochromic RBCs (red blood cells) and platelet in clumps. The reticulocyte and haptoglobin values were also suggestive of hemolysis. Subsequently, the clinical course was complicated with a fall in hemoglobin, thrombocytopenia, and neutrophilic leukocytosis with toxic changes which led us to initiate the workup for sepsis and TMA (thrombotic microangiopathy). Urine microscopic examination showed 20–22 RBCs/HPF (high power field), few bacteria and granular casts. Her coagulation profile was normal throughout the stay. The renal
| Parameters | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 9 | 6 weeks later |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|---------------|
| CBP Hb (g/dL) | 15    | 13.6  | 9.8   | 8.9   | 9.5   | 9.4   | 9.2   | 8.7   | 10.4          |
| Hct (%)     | 39.8  | 36.7  | 28.6  | 26.1  | 27.8  | 27.2  | 27.8  | 28    | 29.4          |
| TC (×10^9/L)| 19.2  | 13.6  | 11.7  | 11.7  | 9.5   | 10.3  | 11.7  | 10.4  | 8.6           |
| DC (%) N/L/M| 83/9/6| 85/12/2| 87/11/1| 88/9/4| 88/7/3| 88/8/3| 77/14/4| 73/18/4| 82/10/4       |
| Platelet (×10^9/L) | 54    | 150   | 105   | 50    | 70    | 72    | 129   | 181   | 192           |
| PS          | Normocytic normochromic (NCNC) | No hemolysis/neutrophilic leukocytosis with toxic change, platelets in clumps | No parasites | No atypical cells | Reticulocyte 4% | NCNC, few schistocytes/echinocytes | NCNC, No abnormal cells |
| Urine examination | RBC-20 to 22/HPF; WBC-2 to 3/HPF, Granular casts 3+, Protein 2+, Bacteria 2+ | RBC 2-3/HPF | Protein 1+ | No parasites | No atypical cells | NCNC, No abnormal cells |
| Blood glucose (mmol/L) | 8.8  | 8.4  | 8.5  | 11.0  | 14.2  | 10.6  | 9.7   | 4.8   | 5.7           |
| LFT         |        |       |       |       |       |       |       |       |               |
| TB (mg/dL)  | 8.9   | 17    | 12    | 10.6  | 7.2   | 5.2   | 1.9   | 1.6   | 0.9           |
| DB (mg/dL)  | 4.3   | 9.4   | 6.2   | 4.2   | 3.6   | 3.8   | 0.6   | 0.9   | 0.3           |
| AST (U/L)   | 940   | 655   | 277   | 167   | 108   | 104   | 62    | 19    | 16            |
| ALT (U/L)   | 379   | 240   | 124   | 124   | 199   | 192   | 108   | 50    | 18            |
| RFT         | B. Urea (mg/dL) | 41    | 109   | 180   | 218   | 247   | 237   | 214   | 90            |
| S. Cr (mg/dL) | 0.9  | 2.4   | 3.4   | 4.3   | 4.5   | 4.5   | 3.8   | 1.9   | 0.9           |
| Serum Electrolytes (mEq/L) | 132 | 126   | 121   | 119   | 135   | 132   | 139   | 139   | 138          |
| Na+         | 132   | 126   | 121   | 119   | 135   | 132   | 139   | 139   | 138          |
| K+          | 4.6   | 4.34  | 4.9   | 4.6   | 5.1   | 4.9   | 4.5   | 4.7   | 3.2          |
| Cl−         | 101   | 93    | 83    | 87    | 104   | 108   | 107   | 109   | 108          |
| LDH (U/L)   | 1018  | 4209  | 2140  | 2040  | 1044  | 977   | 674   | 403   | 224          |
| FDP         | Negative | Negative | Haptoglobin − 0.28 g/L | Plasma fibrinogen (mg/dL) | 214 |
| PT (seconds)/INR | 12/Normal | 20  | 2140 | 2140 | 2140 | 2140 | 2140 | 2140 | 2140          |
| aPTT (seconds) | 12/Normal | 14.4/Normal | 12.2/Normal | Thrombin time (seconds) | 17.6 |
| Culture and sensitivity | Urine – no growth | Blood – no growth | | | | |
| Serum ferritin (µg/dL) | | | | | | | | | |
| Viral markers | WIDAL not suggestive of enteric fever | Dengue – NS1 Ag/Ig G Ab – Negative | | | | |
|                   | Malaria – negative | HIV/HBSAg/Ig G Anti HAV/HCV/HEV – Negative | | | | |
| ICT/DCT         | Negative | Negative | Negative | Negative | Negative | Negative |
| Flow cytometry for PNH | | | | | | | | |
function continued to worsen, however she responded to diuretics. Supportive measures were given, she was on broad spectrum antibiotics and hypertension was under control. She received intravenous Dexamethasone 10 mg twice daily for 5 days. The persistent conjugated (direct) hyperbilirubinemia following delivery made us to initiate the workup for the infective causes of jaundice. Though there was an improvement in LDH, serum bilirubin, and liver enzymes, the clinical picture was worsening in terms of AKI and low platelet count. Her C3 and C4 levels were normal; anti-nuclear antibodies (ANA) and anti-phospholipid antibody (APLA) also were negative. The workup for immune hemolytic anemia was negative. Ultrasound (USG) abdomen showed mild coarsened liver echoes and signs of bilateral medical renal disease. Since the platelet count did not show any significant reduction and serum creatinine was steadily rising, she was planned for plasma exchange in discussion with nephrologist and immunologist. Meanwhile, the sepsis and febrile panel (as peripheral smear showed neutrophil leukocytosis with toxic changes and fever on postpartum day 2) workup revealed real-time PCR positive for scrub typhus and other infective etiologies including viral hepatitis were negative. She was started on oral doxycycline 100 mg twice daily for 7 days. A thorough examination did not reveal any eschar at classical sites. She started showing recovery in terms of reduction in the level of serum creatinine and the platelet count started improving 48 hours after starting doxycycline. Plasma exchange was deferred, and she was discharged after 11 days of hospital stay. Arterial blood gas analysis revealed mild metabolic acidosis in the immediate postpartum period however the Glasgow coma scale (GCS) remained 13–15/15 and never required ventilatory support during the entire course of hospital stay. She developed transient hyperglycemia during the hospital stay which required insulin supplementation. At 8 weeks postpartum she was doing well with no residual renal or hepatic dysfunction. The trend of LDH, platelet count, hematocrit, blood urea, serum creatinine, liver enzymes, and serum bilirubin during the hospital stay is given in Figure 1.

**DISCUSSION**

Scrub typhus was first diagnosed in 1899 in Japan and was considered one of the dreaded diseases during the Second World War in pre-antibiotic era. The first outbreak in India was from Assam and West Bengal [8]. Globally, almost 100 billion people are at risk every year and it is more prevalent in the tsutsugamushi belt which extends from Japan to Russia and Australia to Pakistan. Scrub typhus is often under diagnosed even in

![Figure 1: Serial values of liver function test (AST/ALT/bilirubin), hematocrit, and renal function test (blood urea and serum creatinine). (A) AST/ALT/LDH values, (B) Blood urea value, (C) Hematocrit (HCT) values, and (D) Serum creatinine/bilirubin (total and direct).](image-url)
the endemic areas due to a lack of diagnostic facilities. There can be seasonal variation in the incidence of scrub typhus as 80% of the cases of scrub typhus occurs during summer/autumn. Our patient also presented in the later part of summer and our region is an endemic area for scrub typhus. The presentation in pregnant women is similar to non-pregnant state and is characterized by fever, chills, vomiting, abdominal pain, and headache. Table 2 describes the World Health Organization (WHO) diagnostic criteria for scrub typhus and scrub typhus infection criteria (STIC) [10, 12, 13]. As a direct method, real time polymerase chain reaction for the diagnosis of scrub typhus has more sensitivity and specificity compared to indirect methods used however cost is the limiting factor [12]. Eschar formation, 5–20 mm necrotic lesion at the site of bite or ulcer with regional lymphadenopathy is the single most important clue for the diagnosis but their presence can be highly variable (7–97%) [7]. The common sites are groin, axilla, chest, and lower back; however the clinical experience of the medical personnel and color of the skin are the factors that influence its recognition. Even in our patient a detailed examination after the diagnosis of scrub typhus could not identify the eschar. Abdominal pain due to vasculitis is common in women with scrub typhus which is likely to get missed in pregnant women as the symptom has a variety of causes. There is evidence for the deposition of O. tsutsugamushi in endothelial cells which is supported by positive immunohistochemistry for its antigen. Almost 30% of the individuals go on to develop one organ dysfunction if untreated and the most common being AKI or acute hepatic failure (AHF) [7, 11–15].

Rajan et al. reviewed a total of 738 women diagnosed to have scrub typhus over the period of two years and among them 33 were pregnant (4.5%). Scrub typhus was diagnosed based on the presence of clinical symptoms with eschar or clinical symptoms with antibody testing. The presentation was variable common being respiratory discomfort (63%), eschar (51.5%), headache (33%), vomiting (27%), and hepatosplenomegaly (12%). Though maternal mortality was less (3%), 70% of pregnant women required intensive care therapy for survival. The poor fetal outcome was seen in 51.5% of women in the form of and preterm birth (9.1%) and pregnancy loss (42.4%; including miscarriage and still birth). Duration of illness of >7 days was the independent risk factor for the poor fetal outcome with the odds ratio of 2.46 (95% CI 1.6–85.9, p < 0.01) [10].

A retrospective study of 42 pregnant women diagnosed to have scrub typhus from South India had documented various adverse maternal and perinatal outcomes. The pregnancy loss across all trimesters was 33% and the rate in each trimester was 67%, 38%, and 20%, respectively. All of them who had pregnancy loss were febrile at the time of presentation and eschar was found in 50% of them. The pregnancy loss in patients infected with scrub typhus was significantly higher in their study when compared to women without scrub typhus infection (33% vs. 2.8%; p < 0.001) [11].

Co-infection with other organisms can occur even with scrub typhus and there have been case reports of co-infection with hepatitis E, malaria, dengue, and Leptospira [16]. Generally, co-infections are the main reason for the late diagnosis of scrub typhus unlike in our case where the

Table 2: Diagnostic criteria for scrub typhus [10, 13]

| I | WHO criteria for diagnosis of scrub typhus [10] |
|---|---|
| Clinical description | • Acute onset fever along with headache, sweating, conjunctival injection, with dull macular popular rash over the trunks and extremities  
• Presence of a primary “punched out” skin ulcer (eschar), where the bite occurs  
• Defervescence within 48 hours following tetracycline initiation |
| Laboratory criteria for diagnosis | • Isolation of O. tsutsugamushi by inoculation of patient’s blood in white mice<sup>a</sup>  
• Serology detection scrub typhus IgM 1:100 or higher by EIA by ELISA<sup>b</sup>  
• 1:32 dilution or higher by IP<sup>c</sup>  
• 1:10 dilution or higher by indirect IF<sup>c</sup> |
| Case classification: | Suspected: a case that is compatible with the clinical profile  
Confirmed: a suspected case with laboratory confirmation |

| II | The scrub typhus infection criteria (STIC) [13] |
|---|---|
| Positive in vitro isolation of O. tsutsugamushi using cell culture |
| Admission IgM cutoff titer of ≥1:12,800 |
| Four fold rise in IgM titer in paired sampling |
| Positivity of sample using PCR methods which targets minimum two genes for amplification |

WHO: World Health Organization, IgM: immunoglobulin M; EIA: enzyme immunoassay; IP: immunoperoxidase; IF: immunofluorescence.
<sup>a</sup>Not used in the case definition.
<sup>b</sup>Kit used: PanBio Ltd, Brisbane, Australia, PCR-polymerase chain reaction
presentation was like severe PE/HELLP/AFLP. Recovery following delivery is the rule in those conditions, but our patient went on to develop hemolytic anemia and AKI in the postpartum period. Though it is not uncommon for HELLP syndrome to worsen in the postpartum period, the degree of AKI (rising serum creatinine up to 4.5 mg/dL) and fall in platelet count prompted us to look for other causes. Initially, the workup and management were started in terms of TMA, however the persistent direct hyperbilirubinemia prompted us to evaluate for the infective causes of jaundice. When the clinical deterioration warranted plasma exchange, she was started on oral doxycycline and she responded in terms of serum creatinine and platelets returning to normal in 2–3 days made us conclude it as a case severe PE/HELLP syndrome coexistent with scrub typhus. There have been few case reports on scrub typhus masquerading as HELLP syndrome and acute liver failure in pregnancy [17, 18]. The pathophysiological hallmark of scrub typhus is focal or disseminated vasculitis [19]. The platelet aggregation and neutrophil proliferation which happen as a result of endothelial disruption are because of proliferation of the organisms in the small vessel endothelium. In the peripheral smear of our patient, there was neutrophilic leukocytosis and platelets were in clumps which were mistaken for sepsis and thrombocytopenia of usual causes in pregnancy. The end-organ damage could be due to micro-infarction which might have been responsible for AKI. There was a prospective observational study by Koshy et al. which explored the prevalence of anti-nuclear (ANA) antibodies in patients with scrub typhus. The prevalence was found to be 57.3% (n = 48) when compared to other febrile illnesses (15%, n = 9) and this difference was statistically significant (p < 0.001). Acute respiratory distress syndrome (ARDS) (57.3%) and AKI (36%) were the prevalent complications in their study, and ANA positivity was correlated with ARDS, AKI, and hepatic dysfunction compared to other morbidities. Anti-nuclear antibodies positivity levels in such patients tend to decrease during the recovery phase, however, our patient did not have ANA positivity even during the clinical course of AKI. There is evidence for such ANA positivity in other infections like hepatitis B, malaria, and tuberculosis which is known as epiphenomenon but the prevalence is very high in scrub typhus because of its pathogenic effect on vascular endothelium. None of the patients with ANA positivity during scrub typhus infection went on to develop autoimmune disease in their study [17].

The drug of choice in rickettsial infection is doxycycline, however during pregnancy azithromycin is a reasonable alternative. We used doxycycline in our patient as she had delivered by the time the diagnosis was made. Azithromycin is found to be useful in these case series as it is very efficient in penetrating polymorphonuclear leukocytes and macrophages which are the target cells in scrub typhus [15]. The widespread availability of diagnostic tests and awareness to evaluate for scrub typhus in recent days when they present with acute febrile illness coupled with appropriate antibiotic therapy and supportive measures have improved the overall outcome. Careful examination to look for eschar in such patients will help to identify the infections more effectively. However, in our case, neither fever nor eschar was found during the whole course of the hospital stay. Progressively worsening direct hyperbilirubinemia prompted us to send the markers for infective causes. Though there were signs of improvement in terms of fall in LDH, serum bilirubin, the worsening AKI prompted us to initiate plasmapheresis. However, complete recovery in the patient following doxycycline is the key point in our case. The present case is an example of early onset severe PE coexistent with scrub typhus with an atypical presentation and this gave us an important lesson not to miss the common infective causes in developing countries.

CONCLUSION

HELLP syndrome and AFLP are medical emergencies which necessitate termination of pregnancy as the ultimate management. However, preparing for delivery is a challenge in the presence of AKI and coagulopathy. Often, recovery is the rule following delivery and some of them would go on to develop TMA and end up in severe renal injury which might warrant plasma exchange. Even though clinical diagnosis of these obstetric conditions may appear straightforward, it is important not to overlook infective causes in low middle-income countries, especially in atypical presentation.

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Author Contributions
Sasirekha Rengaraj – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Veena Ranjan – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Shree Bharati – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Kirti Girish Deodhare – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Sanghamitra Hazarika – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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