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Atypical Presentation of Rocky Mountain Spotted Fever in Pregnancy

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Abstract

Rocky Mountain spotted fever (RMSF) is a common tick-borne disease and can have variable presentation with potentially fatal outcomes when untreated. We describe an atypical presentation of RMSF in the third trimester. A 37-year-old multiparous woman at $31^{0/7}$ weeks' gestation presented normotensive with headaches and fever but no rash or significant tick exposure. She was initially treated for atypical hemolysis, elevated liver enzymes, and low platelet count syndrome but further decompensated, requiring intensive care unit transfer, intubation, and emergent delivery. Doxycycline administration was associated with marked improvement with no significant sequalae to mother or infant. Later convalescent serologies were positive for RMSF. RMSF is a clinically challenging diagnosis in pregnancy. Given significant morbidity and mortality associated with delayed treatment, high suspicion in endemic areas is needed, and prompt antibiotic use with doxycycline should be administered.

Keywords
- Rocky Mountain spotted fever
- pregnancy
- tick-borne
- infections
- doxycycline

Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii*, is the most common tick-borne rickettsial disease in the United States.[1] Fatal outcomes have been reported in up to 20% of untreated cases and 5% of treated cases.[2] The diagnosis of RMSF can be clinically challenging due to nonspecific and highly variable initial symptoms as well as limited diagnostic value of serologic testing. The classic triad of fever, headache, and rash is only observed in 3% of patients with RMSF in the first 3 days of illness.[1]

The diagnosis of RMSF in pregnancy poses a unique challenge as a number of the clinical manifestations, such as myalgias, fatigue, nausea, vomiting, headache, and abdominal and back pain are common in pregnancy, which may delay further diagnosis. Severe manifestations such as respiratory distress, acute renal failure, and neurologic changes are associated with other pregnancy-related diseases including preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.[3] Furthermore, the standard of care treatment for RMSF is doxycycline and chloramphenicol, which were formerly classified as Class D in pregnancy and are generally avoided in pregnancy.[1]

We describe a case of an atypical presentation of RMSF in pregnancy successfully treated with doxycycline.

Case

A 37-year-old gravida 2, para 1 previously healthy woman was referred to our hospital during the summer of 2019 at $31^{0/7}$ weeks' gestation due to severe headaches for a week and a fever of 38.9°C in her obstetrical office. Her pregnancy was complicated by a history of migraines, though this headache presented differently from her typical migraine. She described this headache as a severe frontal headache with mild photophobia and phonophobia that was not

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relieved with over-the-counter medication. It began during travel to Washington state in the prior week, most of which was spent in Seattle. However, she did note a brief walk in the woods but reported no tick bites, signs of tick bites, nor contact with any animals other than her own dog which showed no change in behavior. She worked as an art curator in North Carolina. Over the few days prior to admission, she developed night sweats, chills, sweating, dyspnea, and one episode of diarrhea.

On admission, she continued to report unremitting headache. No rash, acute meningeal signs, evidence of lymphadenopathy, nor focal neurological deficits was noted. Her vital signs were normal, and fetal status was reassuring. However, laboratory assessment was significant for normal white blood cell (9.2×10^9/L) with bandemia (23%) noted on manual differential, transaminitis (aspartate transaminase 104), anemia (lactate dehydrogenase 326), hemoglobin (9.7 g/dL), proteinuria (3+ on urine analysis with P:C ratio of 1,203 mg/g), and thrombocytopenia (76×10^9/L). No prior history of thrombocytopenia or proteinuria was evident on her prenatal records. Infectious urine analysis and respiratory panel (including influenza) were negative. She was acutely treated for atypical HELLP syndrome, despite being normotensive, with betamethasone, intravenous (IV) fluids, and IV magnesium, while a further infectious workup was pending given her fever. Haptoglobin was normal, and a manual peripheral smear showed normal platelet counts and no evidence of schistocytes, hemolysis, or platelet clumping. Magnesium was then discontinued, with further infectious workup pursued, including lumbar puncture and a noncontrast brain magnetic resonance imaging (MRI). She was started on empiric IV vancomycin and meropenem for unknown infectious etiology.

Six hours after antibiotic initiation, her vital signs worsened with continued fever, severe tachypnea, tachycardia, and a new oxygen requirement (89% on room air to 95% on 3-L nasal cannula). Because of this acute decompensation, she was transferred to the intensive care unit (ICU).

Overnight, the fetal heart rate displayed repetitive decelerations to the 70 to 80 and the patient developed respiratory distress and desaturation quickly after (respiratory rate 30, heart rate 111, SpO_2 97% on 4-L nasal cannula). The decision was made to proceed with intubation and urgent cesarean section due to maternal and fetal distress. She tolerated the surgery well and was transferred back to the ICU. Neonatal condition was stable with a weight of 1,775 g and Apgar scores 9 and 9. The neonate was taken to the neonatal intensive care unit (NICU) due to gestational age.

The patient was started on doxycycline immediately after vancomycin was discontinued. RMSF became the presumed diagnosis due to the clinical criteria of headache, fever, and malaise, laboratory findings notable for thrombocytopenia, transaminitis, acutely worsening disease, and cerebrospinal fluid analysis consistent with aseptic meningitis. Tissue biopsies were not taken at the time of acute infection; however, the placenta was sent for pathologic evaluation. Her cerebrospinal fluid studies were consistent with aseptic meningitis. She was noted to have significant improvement with doxycycline treatment, although her postpartum course was complicated by acute kidney injury, thrombocytopenia, ileus, and stable transaminitis. Her brain MRI was unremarkable, and she was extubated 3 days later with a normal neurologic examination. She was discharged home on postoperative day 6.

The acute RMSF antibody, which resulted after her decompensation and delivery, was negative. Microabscesses seen on pathologic evaluation of the placenta were concerning for *Listeria* infection. However, placental cultures for *Listeria* and *Rickettsia* were negative. Rickettsial placental immunohistochemical (IHC) staining was performed and was also negative. The patient's clinical syndrome and improvement on doxycycline were consistent with RMSF; her convalescent serologies were positive (> 1:256). The infant overall did well in the NICU and showed no evidence at delivery or in the neonatal period of RMSF or *Listeria* infection.

Discussion

We present an atypical case of RMSF in the third trimester in a patient who was successfully treated with doxycycline. Literature around RMSF during pregnancy has been limited.[3–10] In endemic regions, especially eastern and south-central United States, the presence of a fever, transaminitis, thrombocytopenia, and rash in any patient with a history of a tick bite, pregnant or not, presumes the diagnosis, and empiric therapy should be started. However, in the setting of pregnancy, even in an endemic area, the differential diagnosis for fever with transaminitis and thrombocytopenia includes a number of other infectious diseases (rubella, streptococcal toxic shock syndrome, and Epstein–Barr virus) as well as immunologic and rheumatologic causes (immunologic thrombocytopenic purpura). In the pregnant population, severe preeclampsia and HELLP can also present with transaminitis and thrombocytopenia.[3]

RMSF can be promptly suspected with the presentation of a petechial rash on the palms and soles 2 to 5 days after the onset of fever.[2,8] However, up to 20% of cases present with an atypical or absent rash.[1,2] This is the first case to our knowledge to report RMSF in pregnancy without a significant rash or tick history. It is possible that a rash may be less likely in pregnancy, but these data are limited. Given that fatal outcomes have been reported in up to 20% of untreated cases and 5% of treated cases, absence of a rash but appropriate clinical picture should not exclude RMSF.[2]

The pathophysiology during pregnancy and the potential for vertical transmission are still unknown. In a series of four cases in Mexico, RMSF infection in three patients infected during the first trimester led to abortion, likely related to hypotension and placental ischemia. The fourth patient was diagnosed during the third trimester with no sequelae to either mother or fetus.[6] In one pregnancy affected by Brazilian spotted fever, autopsy results confirmed positive IHC staining for rickettsial antigen in maternal tissue but not observed in fetal tissues.[8]

The microabscesses in the placenta in this case posed an interesting conundrum. Though all cultures were negative, this finding at least indicates placental inflammation. In prior literature, pathologic evaluation of the placenta has not noted evidence of RMSF in the placenta.[3,5] At this time, there is not enough evidence to suggest RMSF crosses the placenta, and there are no reported cases of fetal disease; murine studies have not shown evidence of vertical transmission.[3] However, thorough placental pathology and microbiology assessment should be considered in suspected RMSF.

Prompt and timely treatment with doxycycline significantly limits the morbidity and mortality of RMSF in both children and adults.[1] However, tetracycline use in pregnancy has been limited due to classification as category D and concern for teeth and bone malformation in the fetus and hepatotoxicity and pancreatitis in the mother.[2,11] Chloramphenicol had been historically recommended for pregnant patients with RMSF despite the risk of gray baby syndrome.[12] There is growing evidence that the use of doxycycline in pregnancy is safer than previously thought.[11] Fetal teeth discoloration may be due to calcification occurring after delivery; therefore, short courses of doxycycline may be acceptable.[3] Prior case studies have also demonstrated no significant sequelae to fetus or mother with the use of doxycycline in the third trimester.[3,6] A recent review noted no evidence of any human teratogenicity, permanent teeth staining, hepatotoxicity, nor permanent inhibition of bone growth effects with the use of doxycycline in pregnant patients. Initial studies demonstrating adverse effects examined significantly higher doses of other IV tetracyclines which are no longer used today.[11] Therefore, doxycycline should be recommended as the drug of choice for RMSF therapy in pregnancy, particularly in severely ill patients prior to confirmatory testing.[2]

RMSF is a clinically challenging diagnosis in pregnancy given variable presentation and other likely differential diagnoses. Many patients do not report any exposure risk to ticks, and atypical presentations can occur as in this case. Avoidance of tick-infested areas, proper use of clothing and repellants, and awareness of local prevalence is important to prevent this potentially fatal infection.[2] Doxycycline use may have important implications in the setting of pregnant patients not improving with traditional broad-spectrum antibiotics, and potentially decrease the risk of prematurity due to iatrogenic delivery. Given the potentially dire implications in pregnancy, providers in endemic areas should consider RMSF in the differential of atypical presentations in pregnant women and those with a fever of unknown origin.

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Conflict of Interest
None declared.

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