Case Report: Co-Infection of *Rickettsia rickettsii* and *Streptococcus pyogenes*: Is Fatal Rocky Mountain Spotted Fever Underdiagnosed?

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Abstract. Rocky Mountain spotted fever, a tick-borne disease caused by *Rickettsia rickettsii*, is challenging to diagnose and rapidly fatal if not treated. We describe a decedent who was co-infected with group A β -hemolytic streptococcus and *R. rickettsii*. Fatal cases of Rocky Mountain spotted fever may be underreported because they present as difficult to diagnose co-infections.

INTRODUCTION

Rocky Mountain spotted fever (RMSF) is a tick-borne bacterial disease caused by *Rickettsia rickettsii*. It can be rapidly fatal if not treated appropriately with doxycycline in the first five days of illness.¹ Most patients with RMSF have non-specific febrile signs and symptoms, making it difficult to differentiate this disease from more common diseases. Patients typically seek treatment early in the course of disease, and death frequently occurs because of treatment delay secondary to initial misdiagnosis.¹ Delay is usually caused by variable signs and symptoms, the fact that *R. rickettsii* is an intracellular bacterium, and because acute diagnostic testing is challenging when standard procedures are used.² We report a case of atypical presentation, demonstrate another way in which fatal cases are underreported, and demonstrate the importance of prompt empiric treatment with doxycycline in disease-endemic areas, even when other causes of illnesses seem more likely.

CASE REPORT

On April 7, 2012, a 43-year-old Native American man with type 2 diabetes and hypertension, came to a Phoenix, Arizona, area emergency department on the fourth day of influenza-like symptoms, including subjective fever, malaise, diarrhea, nausea, vomiting, and back pain. At the initial examination, he had severe lower back pain radiating to the lower extremities and he was afebrile (temperature = 37.0°C) and hypotensive (blood pressure = 96/55 mm Hg).

Laboratory evaluations showed abnormal liver function (aspartate aminotransferase level = 309 U/L, alanine aminotransferase level = 185 U/L, bilirubin level = 8.81 mg/dL), hyponatremia (131 mmol/L), and thrombocytopenia (28,000 cells/cm³). The following values were noted: hematocrit = 55.3%, leukocyte count = 5,700 cells/cm³ with 43% bands, 42% segmented neutrophils, 7% lymphocytes, and 0.9% monocytes. His initial differential diagnosis was sepsis with disseminated intravascular coagulation and possible thrombotic thrombocytopenic purpura.

Because of this diagnosis, he was given ceftriaxone, fluid boluses, and hydromorphone for pain and urgently transferred to a tertiary care center for higher level care on the same day. At admission, he was hypotensive and aggressive crystalloid fluid resuscitation was initiated. Physical examination after transfer showed progressing purpurral skin changes on the chest, petechial lesions on the hard palate, and acrocyanosis. On the fourth day of his illness, blood and urine cultures were obtained and he was given empiric antibiotics that included ampicillin/sulbactam, ceftriaxone, gentamicin, and doxycycline. The patient was considered to be in septic shock and etiologies under consideration included RMSF, invasive pneumococcal disease, *Listeria* infection, and plague.

Over the course of 24 hours, he showed decompensation and signs of multi-system organ failure, including respiratory distress requiring intubation, renal failure, coagulopathy, severe acidosis, and cardiovascular collapse requiring vasopressors. On April 8, 2012, the fifth day of symptoms, his condition decreased precipitously, life supportive measures were removed, and the patient succumbed to this infection on the same day.

Samples collected on April 7, 2012 were sent to the Arizona Department of Health Services and the Centers for Disease Control and Prevention (CDC) for additional testing due to the unknown etiology of this patient's rapidly fatal infection. His serum was positive by polymerase chain reaction (PCR) for *Rickettsia rickettsii* and at 24 hours his blood culture demonstrated 4+ growth of *Streptococcus pyogenes*. Additional testing at the CDC demonstrated that the blood sample was also positive for *S. pyogenes* by PCR.

DISCUSSION

There are several factors that make this case different from previously reported cases of RMSF, and this case may have been caused by the nature of the co-infection with *S. pyogenes*. First, the timeline alone is unusual. Patients with RMSF typically seek treatment early in the course of symptoms, and although the symptoms of the patient were initially described as influenza-like and he had been working at his job up until the day of admission, his initial vital signs and laboratory values demonstrated findings of late RMSF and septic shock. In addition, although RMSF can progress rapidly, it is typically treatable within the first five days of symptoms. This patient received treatment with doxycycline on the fourth day

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of illness and it did not stop the progression of disease. The date of death was also sooner than expected for RMSF. The median time to death for RMSF is 10 days, and the death of the patient on the fifth day of symptoms was atypical.³

This case was a clinical challenge because there was no reported exposure to ticks or a tick bite and the initial primary findings were influenza-like symptoms and back pain. The patient stressed that his primary concern was the back pain, which he initially attributed to exacerbation of chronic musculoskeletal pain from his employment. Later that day, his condition worsened and was consistent with signs and symptoms of sepsis. Rocky Mountain spotted fever has been known to show abnormal coagulation⁴ and liver transaminase⁵ laboratory findings. The clinical team astutely sent a blood sample to the Arizona Department of Health Services and CDC for additional testing because of the rapid death of the patient five days after onset of influenza-like symptoms.

The real-time PCR assay used at CDC to confirm the diagnosis of RMSF in this patient has improved sensitivity for detecting *R. rickettsii* in comparison with the traditionally used nested-PCR method and maintains the high analytical and clinical specificity of the previously used method.⁶

Rickettsia rickettsii does not grow in routine blood cultures and without this additional scrutiny by using sensitive laboratory testing, RMSF would not have been identified; only the pre-mortem positive blood culture for *S. pyogenes* would have been identified this organism as the etiologic agent of his sepsis. This case reinforces the need for rapid treatment with doxycycline when RMSF is considered, and that confirmation of another diagnosis does not rule out the possibility of RMSF.

Other reports have demonstrated that fatal RMSF cases are underreported,^{7,8} and this type of co-infection may demonstrate another reason why a fatal case would go undiagnosed. Serologic results are not likely to be positive for a patient who dies on the fifth day of symptoms, and a specialized diagnostic test such as PCR may not be pursued in cases that have positive cultures for another pathogen. It is possible that other patients had co-infections but never had PCR laboratory confirmation for RMSF, only blood cultures. However, the magnitude of this occurrence is currently unknown and future investigation is needed.

The exact pathogenesis of death of the patient is also unknown. Tissue samples from this patient were not available for testing. The time course seems more consistent with sepsis caused by *S. pyogenes*. Cases of infection with *R. rickettsii* cause severe endothelial damage that begins early in the course of illness.⁹ It appears plausible that vascular damage caused by *R. rickettsii* may have served to facilitate bacteremia with the second pathogen, and that sepsis caused by *S. pyogenes* was the cause of rapid deterioration and death. Another possibility may be that the combined infection may

have become overwhelming and untreatable sooner than either pathogen would have alone.

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