Red herrings and rocky mountains: a case of unsuspected rocky mountain spotted fever in a critically ill patient

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Abstract

Rocky Mountain Spotted Fever is a tick-borne illness caused by Rickettsia rickettsii that can rapidly progress to irreversible fatal outcomes, especially with delayed treatment. Diagnosis of this disease can be difficult given its initial non-specific presentation that can easily be mistaken for other community-acquired illnesses or non-infectious etiology. This case was also confounded by a red herring associated with the limitation of unknown diagnostic tests. Here we report a 62-year-old male who presented for three days of altered mentation, fever, and significantly elevated blood alcohol level (0.372 WT/VOL). Relevant findings on initial ED evaluation include leukocytosis (11.5 K/uL), lactic acidosis (3.2 mmol/L), AKI (Cr 3.04 mg/dL, from baseline 0.8 mg/dL), transaminitis (AST 145 U/L, ALT 57 U/L). Patient was admitted to intensive critical care, started on phenobarbital taper for alcohol withdrawal, and concomitantly treated with vancomycin and cefepime for broad sepsis coverage. An initial tick-borne infection panel resulted on hospital day (HD) 1 and was negative, and an atypical infection was believed to be ruled out. Over the next three days, the patient rapidly deteriorated into acute respiratory failure requiring rapid sequence intubation, acute renal failure started on renal replacement therapy, septic shock, thrombocytopenia, and acute deep vein thrombosis. Patient was finally started on doxycycline on hospital day 3 after an unidentified rickettsial panel yielded high titer immunoglobulin M and G for RMSF. Patient fortunately improved with extended doxycycline treatment and was able to be discharged, though now with persistent peripheral neuropathy, ataxia, and short-term memory deficits. This case serves as a reminder of the high mortality outcome for delayed RMSF treatment. In addition, while clinicians strive to maintain broad differential, it is just as important to develop a structured approach to ensure accurate interpretation of clinical data and familiarity with the limitations of various diagnostic tests.

Keywords: Rocky Mountain Spotted Fever, critical illness, renal failure

Introduction

Diagnosis in critically ill patients can be especially challenging, as these patients can present with multi-organ dysfunction, encephalopathy, preventing history gathering, and acute illness that requires decisive action before making a definitive diagnosis. In these settings, a broad differential and work-up is often required. Fortunately, most medical intensive care unit (ICU) admissions will likely involve commonly encountered illnesses such as sepsis, respiratory failure, and toxidromes such as alcohol withdrawal, allowing for the development of algorithmic resuscitation and management guidelines. Indeed, an "Occam's Razor" approach suggests that the simplest (and perhaps most common) pathology is most often correct. However, physicians need to keep an index of suspicion for atypical pathologies, especially when a patient's presumed diagnosis and clinical course do not align. The desire to avoid unnecessary diagnostic testing, overly broad treatment, and reduce healthcare

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costs has emphasized the utility of pre-test probability and other heuristics to help focus medical care. Nevertheless, the margin of error in critical illness is small for diagnostic error, as missed diagnoses may rapidly result in morbidity and mortality if appropriate treatment is not initiated.

Rocky Mountain Spotted Fever (RMSF) is an uncommon but potentially fatal tickborne illness caused by the bacterium *Rickettsia rickettsii*. It often presents as a viral syndrome and can overlap with other infectious or hematological pathologies.[1] Definitive diagnosis requires specific molecular testing, which takes time to result and can be difficult to interpret in an acute setting. Here we present a case of RMSF in a critically ill patient that was masked by multiple, competing diagnoses.

Case Report

The patient is a 62-year-old male with a past medical history of heavy alcohol use (about a fifth of bourbon per day), deep vein thrombosis and pulmonary embolism (diagnosed 9 months prior with uncertain anticoagulation adherence), prostate cancer, gastroesophageal reflux disease, and hyperlipidemia who presented for altered mental status. On the day of admission, he had been confined to his couch for several hours and had an episode of incontinence. Per the patient's spouse, he had stopped drinking 3 days ago due to malaise. Admission vitals were notable for tachycardia (HR 134), fever (TMax 103 F), and hypoxia (SpO2 88% on room air) with blood pressure within normal limits (127/76 mmHg). Admission investigations revealed leukocytosis (11.5 K/uL), lactic acidosis (3.2 mmol/L), elevated creatinine consistent with AKI (Cr 3.04 mg/dL, from baseline 0.8 mg/dL), transaminitis (AST 145 U/L, ALT 57 U/L) without hyperbilirubinemia (total bilirubin 0.9 mg/dL), and hyperammonemia (35 umol/L). Urine drug screen was positive for benzodiazepines (presumptive positive from recent administration), and urinalysis with white blood cells and numerous bacteria. Chest x-ray showed atelectasis versus scarring at the right lung base. A head computed tomography (CT) scan did not reveal an acute intracranial abnormality, and CT abdomen and pelvis showed hepatic steatosis without acute findings. The patient was treated for sepsis with 30 ml/kg fluid resuscitation, ceftriaxone, and linezolid (given renal function) with a suspected urinary source. Given concern for alcohol withdrawal, he had been started on the Clinical Institute Withdrawal Assessment (CIWA) protocol with as-needed IV midazolam, with transition to phenobarbital per critical care consult upon admission to ICU.

The following day (hospital day (HD) 1), the patient arrived at the ICU from the emergency department for tachypnea with RR 50–60 and encephalopathy. Additional phenobarbital was given with improvement in agitation and respiratory rate. A spot electroencephalogram (EEG) was performed, which was negative for epileptiform activity. Linezolid was discontinued given a negative MRSA nasal swab and ceftriaxone was broadened to cefepime. A petechial rash had been noted on his hands and feet by the admitting team. An RPR and tickborne illness panels were ordered to further assess the rash. However, given his encephalopathy, history of alcohol intoxication, and the timing of abrupt alcohol cessation, his main etiologies were considered to be alcohol withdrawal and sepsis with a urinary source, with skin findings attributed to spontaneous microhemorrhage in the setting of thrombocytopenia and presumed coagulopathy. Lumbar puncture was not obtained at this time given thrombocytopenia and recent apixaban use. Of note, he had multiple recent presentations with alcohol intoxication (with a blood alcohol level up to 0.372 WT/VOL) and concern for withdrawal in the setting of consuming a bottle ("fifth") of hard liquor per day. His thrombocytopenia, which had been borderline low previously, was attributed to marrow suppression from alcohol consumption and suspected failure to thrive from associated malnutrition. A heparin drip was continued for an acute bilateral lower extremity deep vein thrombosis noted on the venous doppler ultrasound. His hyperammonemia was treated with lactulose, though the CT abdomen and right upper quadrant ultrasound imaging were without findings of cirrhosis. He was continued on intravenous fluids for renal failure (suspected to be pre-renal) and pancreatitis.

On HD 2, the patient continued to decline with worsening renal function, encephalopathy, uremia

(BUN 118), and agitation requiring additional doses of phenobarbital. A tickborne infection panel (testing for *A phagocytophilum, Babesai microti, B. miyamotoi, E. chaffeenis*, and *Borrelia* spp) ordered by the admitting team was negative. Given the decline in renal function and azotemia, dialysis was initiated.

On HD 3, the patient had a further decline in mental status with worsening pulmonary edema and hypoxia, and was subsequently intubated. Hemodynamic instability and vasopressor requirement necessitated a transition to continuous renal replacement therapy (CRRT). In the midst of this clinical decline, and later on HD 3, a rickettsial infection panel (also ordered on admission) resulted with high immunoglobulin titers for RMSF (IgM 1:1024, IgG 1:1024). He was subsequently started on doxycycline (100 mg, IV, q12h). After the initiation of doxycycline, the patient began to improve with transition to intermittent hemodialysis from CRRT on HD 5, extubation on HD 7, transition out of the ICU on HD 8, and discharge on HD 21. He completed a total 16-day course of doxycycline to treat his RMSF. Real function recovered in the outpatient setting and the tunneled dialysis catheter was ultimately removed.

Discussion

Rocky Mountain Spotted Fever is a tickborne illness transmitted predominantly by the American dog tick (*Dermacentro variabilis*), the brown dog tick (*Rhipicephalus sanguineu*), and the Rocky Mountain wood tick (*Dermacentor andersoni*).[2] It is predominant in the southeastern and south-central United States, though it has been reported throughout the contiguous United States.[2–4] It characteristically causes a centripetally spreading maculopapular rash,[3] with severe disease causing hemorrhagic phenomenon (lymphopenia and thrombocytopenia), coagulopathy, transaminitis, acute respiratory distress syndrome, non-cardiogenic pulmonary edema, and acute renal failure.[5]

This case illustrates such challenges in diagnosing tick-borne infection in critical illness and the need for early empiric therapy if such an infection is suspected in a critically ill patient. The incubation period for RMSF ranges from 3 to 12 days after initial contact, with many patients unable to recall the inciting tick bite, further complicating the association of exposure and symptom onset.[6,7] Initial symptoms are similar to a common viral illness and include fever, headahce, and myalgia, with the classic petechial rash typically manifesting 2–4 days after initial fever (though it may be absent in up to 15% of patients).[7,8]

Delayed treatment is associated with increased mortality.[1] A retrospective review of all RMSF cases submitted to the Centers for Disease Control and Prevention from 1981–1998 observed that treatment initiated 5 days after symptoms onset is associated with a high mortality (40–50%).[1] Similar findings were described in a retrospective review of RMSF patients in Arizona, with a higher mortality when treatment was initiated 6 days after symptom onset.[9] Subgroup analysis showed that the case-fatality rate is 44% among patients admitted to the ICU, 71% among patients who were ventilated, and 60% among patients who had renal insufficiency.[9] Doxycycline is the drug of choice and the only viable option for the treatment of RMSF. Doxycycline should be empirically initiated for suspected RMSF cases, especially in high-prevalence regions during spring and summer seasons when RMSF transmission is most common.[10] Fortunately, doxycycline is well tolerated with a favorable safety profile, low incidence of allergy, does not require renal or hepatic adjustment, and is not removed by dialysis filters.[11,12] The Wilderness Medical Society guidelines recommend that doxycycline should be continued for at least 3 days after fever resolves and/or evidence of clinical improvement, with a minimum treatment duration of 5-7 days.[13] Chloramphenicol, while technically an alternative therapy, is associated with worse outcomes and is no longer readily available in the United States.[1] Patients who are allergic to tetracycline should either receive the antibiotic with close monitoring or undergo rapid desensitization, depending on the severity of the known allergy.[14] Given the efficacy of doxycycline for RMSF, a lack of clinical response within 48 hours of initiating treatment should prompt investigation of an alternative diagnosis, though critically ill patients may take longer to respond.[7] Finally, once doxycycline is initiated, it is reasonable to complete the entire treatment course unless an alternative diagnosis is definitively made.

An important aspect and potential pitfall of tickborne infection management is the interpretation of diagnostic testing, as illustrated here. Serological diagnosis of RMSF is challenging, time-consuming, and of limited utility in an acute setting.[7] A positive IgG indicates exposure, though this is of little utility in an endemic area where acute and prior exposure cannot be differentiated. Because of this, IgG requires a fourfold increase over 2–4 weeks to confirm acute illness, making it impractical in the ICU. While IgM can indicate an active infection, it may be falsely negative during the initial stages of illness (with antibodies taking 1–2 weeks to be detectable) and cannot sufficiently rule out RMSF.[15–17] While polymerase chain reaction testing for RMSF has been developed, it is not widely available and cannot rule out infection.[14] Thus, while diagnostic testing can support clinical suspicion, it should not delay treatment. The recommended practice, therefore, is to treat empirically for RMSF if there is clinical suspicion of disease.[15,18] At our center, such molecular panels were available, though the availability of such tests likely vary from center to center and may take several days to result (as in this case). Regardless, an overreliance on molecular tests can both delay empiric treatment and falsely rule out RMSF despite clinical suspicion. Given the relatively minimal side effects of doxycycline compared to other antimicrobial agents, empiric initiation of doxycycline in suspected cases is not only safe and reasonable, but potentially lifesaving.[9]

This case exemplifies many of the diagnostic challenges in the ICU.[19] Approximately one-quarter of patients admitted to the intensive care unit can be subject to misdiagnosis, which results in lethal complications a third of the time.[20,21] For example, the patient's initial presentation led to anchoring of the alcohol withdrawal and urinary sepsis as the driving processes. Though these are both common illnesses and contributors to his critical illness, an Occam's Razor approach fell short here. An alternative complex critical illness would be Hickam's dictum, developed by physician John Hickam, which states that patients can have any number of comorbid illnesses, not just the simplest or most likely.[22] Furthermore, early treatment with doxycycline was not initiated. This may be due in part to a recent emphasis on antibiotic stewardship. While antibiotic stewardship is important, it can be misinterpreted as a call to use *fewer* antibiotics rather than to use them *better*.[23] In complex, undifferentiated, critically ill patients with suspicion for multiple infectious processes, less isn't always more (as demonstrated here). Early resuscitation and subsequent rapid descalation should be employed in critically ill patients with suspected infection.[24] Finally, a misapplication of molecular testing contributed to delayed treatment. In our hospital, there is both a tickborne and a rickettsial panel, with the latter panel including RMSF serology. When the tickborne panel resulted immediately and was negative, the team erroneously assumed all tickborne diseases were ruled out. This reflects the ongoing challenge of diagnostic testing, which is more than the availability of a test, but also how to interpret it. ICU settings often involve high volumes of clinical and laboratory data.[25] Intensivists must identify critical information from overwhelming clinical data to guide life-saving treatment decisions, which could make them more prone to cognitive bias and errors.[26] Many adaptive strategies, including group case presentation, clinical simulations, structural formatting of differentials, and reflective collaboration in multidisciplinary teams, are demonstrated to reduce error rates in high-risk scenarios.[19]

In conclusion, delayed RMSF treatment (i.e., beyond 5 days of symptom onset) could lead to rapidly fatal outcomes. If RMSF is suspected or the patient presents with a non-specific viral illness in an endemic area, empiric doxycycline should be considered without waiting for serology or molecular assays. The rash does not always appear in RMSF and can often be a late presentation. More importantly, clinicians should always avoid anchoring and keep a broad differential on initial evaluation or unexpected clinical progression.

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