

# Rhabdomyolysis-induced Acute Kidney Injury Secondary to *Anaplasma phagocytophilum* and Concomitant Statin Use

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## ABSTRACT

We report the case of a patient with rhabdomyolysis-induced acute renal failure occurring in the setting of *Anaplasma phagocytophilum* infection based on the presence of morulae in neutrophils and concomitant statin use. Although the pathogenesis is unknown, we believe the combination of concurrent statin use in the setting of the infection promoted this complication. We describe proposed mechanisms including cytokine activation, alteration of the muscle membrane components, and ionic balance as contributing factors.

## INTRODUCTION

*Anaplasma phagocytophilum* is a tick-borne pathogen that is endemic in the midwestern and eastern United States, although it has been reported in other parts of the world. This obligate intracellular pathogen shows leukocyte-specific tropism, infects granulocytes, and commonly causes human granulocytic anaplasmosis (HGA).<sup>1</sup> Symptoms of HGA include undifferentiated febrile illnesses, rigors, myalgias, and generalized malaise accompanied by leukopenia and thrombocytopenia. Rhabdomyolysis, a disease affecting the integrity of the skeletal muscle, is a rare complication of infection with *A phagocytophilum*.<sup>2-4</sup> Herein, we report a case of rhabdomyolysis in an elderly man living in a tick-endemic area.

## CASE REPORT

An 84-year-old man from northern Wisconsin presented with symptoms including confusion, weakness, and diarrhea. Two days earlier he was admitted to a non-affiliated health care

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facility after his wife found him on the floor exhibiting weakness, confusion, and urinary incontinence. On initial evaluation his temperature was 39.4°C. Initial blood cultures, urine culture, and chest x-ray were all negative. Tests for influenza A and B were negative. A lumbar puncture was attempted twice, unsuccessfully. He was initially treated with ceftriaxone,

based on a presumptive diagnosis of meningitis, but because of persistent fever, his antibiotics were changed to imipenem and vancomycin. Overnight, the patient developed diarrhea and pancytopenia. He was subsequently transferred to our hospital.

Upon arrival and further interview, his wife recalled removing a tick from the patient's right groin approximately 5 days prior to presentation. The duration of the tick attachment was unknown. The patient denied any vision change, headache, neck stiffness, photophobia, nausea, vomiting, or trauma. On initial evaluation, his temperature was 38.4°C, pulse rate was 71 bpm, and blood pressure 161/70 mm/Hg. Examination was significant for memory loss for recent events, round erythematous 1.5-cm rash in the right groin, and the absence of hepatosplenomegaly. He continued to be febrile with wheezing, confusion, and complaints of generalized weakness. Medications on admission included simvastatin 40 mg daily, hydrochlorothiazide 25 mg daily, valsartan 320 mg daily, aspirin 81 mg daily, and warfarin 5 mg daily.

Laboratory studies revealed the following: white blood cell count,  $3.6 \times 10^3/\mu\text{L}$  with neutrophil cytoplasmic inclusions morphologically consistent with *Anaplasma* morulae; platelet count  $57 \times 10^3/\mu\text{L}$ ; estimated glomerular filtration rate 42 mL/min; troponin I 0.5 ng/mL; blood urea nitrogen (BUN) 34 mg/dL; creatinine 1.6 mg/dL; aspartate aminotransferase 220 U/L; alanine aminotransferase 43 U/L; uric acid 6.5 mg/dL, ionized calcium 4.6 mg/dL, phosphorous 3.2 mg/dL; creatine kinase 9299 U/L; and urinalysis with 1+ protein, 3+ blood (without red blood cells present), 1+ leukocytes. Blood, urine, and

stool cultures showed no bacterial growth. Renal ultrasound was normal. Anaplasma antibody <1:64, Babesia Ab <1:16, and Lyme serology were nonreactive. He was treated initially with doxycycline 100 mg intravenous twice daily and intravenous hydration with sodium bicarbonate for rhabdomyolysis. Over the course of the hospitalization, the patient's renal function and mental status improved and he was discharged to a nursing home.

## DISCUSSION

Rhabdomyolysis is a disease characterized by the breakdown of skeletal muscle and the release of electrolytes, myoglobin, and other muscle proteins into the systemic circulation. Acute renal failure is a serious complication that develops in as many as 33% of patients with rhabdomyolysis.<sup>5</sup> Free myoglobin is filtered in the kidney, damaging the nephron as a consequence of renal tubule obstruction and oxidative injury.<sup>5,6</sup> The risk of acute kidney injury in rhabdomyolysis is low, with creatine kinase levels less than 15,000 to 20,000 U/L, but may occur with levels as low as 5000 U/L, especially in the presence of other contributing factors such as sepsis, intravascular volume depletion, acidosis, and renal vasoconstriction.<sup>6</sup> Intravascular volume depletion causes intrarenal vasoconstriction due to activation of the renin-angiotensin, vasopressin, and sympathetic nerves.<sup>6</sup> Other mediators that reduce vascular tone and renal homeostasis include endothelin-1, thromboxane A<sub>2</sub>, tumor necrosis factor  $\alpha$ , and F<sub>2</sub>-isoprostanes;<sup>7,8</sup> nitric oxides are released in response to myoglobin induced oxidative stress.<sup>6</sup>

The etiology of rhabdomyolysis secondary to *A phagocytophilum* infection is still unknown. Proposed mechanisms of rhabdomyolysis caused by other infections include tissue hypoxia, reduced or activated enzymatic responses, and endotoxic effects.<sup>5</sup> Direct invasion of skeletal muscle resulting in rhabdomyolysis has been identified in certain bacterial infections including *Streptococci*, *Salmonella*, and *Staphylococcus aureus*.<sup>9,10</sup> This mechanism, however, is not likely in a case of *A phagocytophilum*, since *in vitro* investigation of *A phagocytophilum*-infected neutrophils showed reduced adhesion to endothelial cells.<sup>7</sup> Additionally, while *Legionella* spp is associated with rhabdomyolysis, it is not found in muscle biopsies, suggesting an alternative cytochemical pathway.<sup>11</sup> Cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1), have been implicated in causing rhabdomyolysis-associated skeletal muscle damage.<sup>12</sup> Though a clear association is lacking, elevation of cytokines involved in the innate immune response and macrophage activation, including gamma interferon (IFN- $\gamma$ ), IL-12, and IL-10 have been described in *A phagocytophilum* infection.<sup>13</sup>

Statin-associated myopathy also may have played a role in this patient's development of rhabdomyolysis. The mechanisms

through which infectious agents contribute to, or exacerbate, statin-induced myositis are not fully understood. Statins are believed to induce myocyte injury through the disruption of membrane components and ionic balance.<sup>11</sup> Additionally, incidence of statin-induced rhabdomyolysis associated with other infectious agents including *Enterococcus faecalis* has been reported.<sup>14,15</sup> In a reported case of myositis with creatine kinase (CK) elevation, both statin use and HGA infection were identified as potential contributing factors.<sup>16</sup>

*A phagocytophilum*, the suspected agent in this case, is transferred by vector host of *Ixodes scapularis* in Wisconsin.<sup>17,18</sup> This tick also serves as the zoonotic vector for *Borrelia burgdorferi* (the cause of Lyme borreliosis) and *Babesia microti* (the cause of babesiosis).<sup>17-19</sup> Genetic variants of *A phagocytophilum* have been reported among isolates collected in Rhode Island, Connecticut, and Washington.<sup>8,20</sup> It has been postulated that disparity in disease incidence, severity, seroprevalence, and manifestation could be due to genetic differences in *A phagocytophilum* strains.<sup>20</sup>

Transmission of the pathogen usually occurs after a minimum of 24 hours of tick attachment and an incubation period 7 to 10 days.<sup>16,21</sup> Though most infections are related to tick exposure, additional transmission modalities may exist including mother to child transplacental transmission and exposure to infected deer blood.<sup>17</sup> Between 1994 and 2005 over 2900 cases of HGA have been reported to the Centers for Disease Control and Prevention (CDC)<sup>22</sup> with a reported incidence of 8.79 per million in Wisconsin.<sup>23</sup> However, more recent active surveillance has shown an incidence of more than 500 per million. Additionally, seroprevalence studies suggest that asymptomatic infection is common, and the principal risk factor for contracting HGA is the length of residence in endemic areas.<sup>17,22</sup>

A presumptive diagnosis of HGA may be made by the presence of unexplained fever, nonspecific symptoms (eg, headache and generalized myalgias), and laboratory values showing leukopenia and thrombocytopenia in resident(s) in an area endemic for the vector.<sup>17</sup> In addition, the observation of granulocytic morulae by experienced pathologists adds weight to the diagnosis. In this particular case, presence of morulae in the granulocytes of blood samples from the patient living in an endemic area was quite relevant. Laboratory diagnosis should not delay treatment, given the rapid progression of this potentially fatal infection.<sup>24</sup> Differentiation between probable and confirmed HGA may be based on case definitions established by Walker et al<sup>25</sup> that include a combination of clinical symptomology and laboratory tests including polymerase chain reaction, blood culture, and demonstration of antibody titers specific for HGA in serum. However, the sensitivity of the various laboratory tests varies with phase of the illness.<sup>24</sup> In our case, the serologic testing was negative for HGA. The false negative result may

be attributable to testing during the first week of illness when sensitivity for this test is at its lowest. Ultimately, the laboratory diagnosis was made based on the presence of infected neutrophils (morulae) identified during differential evaluation of the peripheral blood smear. Laboratory diagnosis based upon blood smear interpretation has a reported sensitivity of 25% to 75%.<sup>24</sup> Confirmed presence of infected neutrophils defined this case as consistent with probable HGA.

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