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The Unusual Suspects: A Curious Case of Acute Kidney Injury: Answers

Jessica L. Stahl¹, Joe Rutledge², and Roberto Gordillo Perez¹

¹Seattle Children's Hospital, University of Washington, Division of Nephrology, 4800 Sand Point Way, Seattle, WA 98105

²Seattle Children's Hospital, University of Washington, Division of Pathology, 4800 Sand Point Way, Seattle, WA 98105

Answers:

1. Figure 1a–b shows red supernatant suggestive of hemoglobinuria or myoglobinuria accompanied by muddy brown cast, many tubular epithelial cells, and few erythrocytes on microscopy, consistent with rhabdomyolysis. In figure 2, we can see necrotic fibers with minimal presence of lymphocytes or histiocytes (marked by arrows in Figure 2a.). Ancillary staining showed moderate diffuse MHC-1 consistent with inflammatory or autoimmune-mediated process, as well as scattered C5b-9 deposition in some myofibers and capillaries.

Fig2a Muscle biopsy with arrows indicating necrotic fibers

2. While the differential diagnoses associated with the initial presentation included prerenal acute kidney injury (AKI), and pigment nephropathy associated with rhabdomyolysis, the development of worsening anemia and thrombocytopenia suggested a burgeoning thrombotic microangiopathy (TMA). The differential diagnoses for TMA is as follows:
 - Shiga toxic E. Coli-hemolytic uremic syndrome (STEC-HUS)
 - Infection/sepsis-related
 - Human immunodeficiency virus, hepatitis A&C, cytomegalovirus, influenza H1N1, Epstein Barr Virus, Streptococcus pneumoniae
 - Malignancy
 - Drugs

Corresponding author: Dr. Jessica L. Stahl, jessica.stahl@seattlechildrens.org, Phone: 206-987-2524 .

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Conflict of interest

The authors declare no conflict of interest

- Quinine, quetiapine, trimethoprim-sulfamethoxazole, chemotherapeutics, tacrolimus, sirolimus, MDMA, cocaine, oxycodone
 - Thrombotic thrombocytopenic purpura (TTP)
 - Macrophage activation syndrome-associated
 - Autoimmune diseases
 - Lupus, scleroderma, antiphospholipid syndrome, immune-mediated necrotizing myopathy, inflammatory myopathy
 - Cobalamin deficiency
 - Complement-mediated hemolytic uremic syndrome (HUS)
3. Initial management in a patient with rhabdomyolysis should focus on hydration and prevention of pigment deposition. With the development of TMA, evaluation and management of the potential etiologies is key[1]. Since STEC-HUS occurs even in the absence of diarrheal illness in about 5% of cases, all patients with HUS should be assessed for the presence of STEC. For possible sepsis management, blood cultures and relevant viral serologies should be obtained early and consideration given to empiric antibiotic therapy until results are available. Coordination with oncology colleagues to discuss the utility of bone marrow biopsy or other investigation for possible malignancy is important to consider prior to initiation of immunosuppressive medications given that the risk of masking malignancy with treatment and that immunosuppressive therapy is the mainstay of management for autoimmune causes of TMA. Screening should be conducted for TMA-associated medications, including those detailed above. Early pheresis is appropriate, as TTP is a possibility, ensuring that an ADAMTS-13 level has been obtained prior to therapy. Macrophage activation syndrome is treated with anakinra (IL-1 antagonist) and inflammatory markers are tracked to determine response to treatment. Other autoimmune etiologies for TMA may be elicited by testing for autoantibodies, to include ANA, Anti-dsDNA, Antiphospholipid, Anti-Scl70, ACA, and RNA polymerase III. Screening for cobalamin deficiency would include homocysteine, methionine, and methylmalonic acid levels.

Assessment for other causes of HUS can include genetic screening, complement studies (C3, C4, complement factors B, H, and I, factor H antibody), and levels of CH50. Laboratory evaluation for terminal complement activation (i.e. C5b-9) has questionable utility as a diagnostic marker, and is unreliable in monitoring response to therapy in complement-mediated HUS as it may remain detectable even in the setting of controlled illness.

Here, blood cultures were negative, bone marrow biopsy was normocellular, ADAMTS13 activity was normal, complement studies were normal, and HUS genetic and serum testing was not suggestive of complement mediated TMA as an underlying cause. His constellation of myositis, heliotrope rash, retinopathy,

and gingivitis with the above muscle biopsy findings with otherwise negative myositis antibodies are most consistent with juvenile dermatomyositis.

Discussion:

Juvenile inflammatory myopathies are a rare, heterogeneous group of autoimmune disorders united by skeletal muscle involvement. The most common of these is juvenile dermatomyositis (JDM), which has a prevalence of 2–4 cases per million children in the US. The vasculopathy associated with JDM is known for causing a variety of cutaneous lesions, particularly the “heliotrope rash”, as noted on this patient’s presentation, as well as malar rash, ulcerations, nail-bed abnormalities, and calcinosis. Gastrointestinal and pulmonary involvement are also common[2, 3]. Other systemic manifestations including pseudo-Purtscher’s retinopathy[4, 5] and JDM-associated MAS[5–7] have been reported as well, but are quite rare.

The renal effects of JDM and other inflammatory myopathies are not well described, but represent an important consideration in the assessment and management of these patients given the potential for added morbidity and mortality. Rhabdomyolysis is an uncommon manifestation of disease despite potentially chronic muscle inflammation and should be managed similarly to other causes of rhabdomyolysis with treatment of the underlying disturbance and attempt to minimize pigment deposition[8]. Renal sequelae in adult inflammatory myopathies are more common than previously thought with AKI and chronic kidney disease reported in about 20% of patients.[8, 9] In those with chronic renal sequelae, membranous nephropathy with immune complex deposition was the most common etiology of renal involvement. To the best of our knowledge, oliguric AKI has not been previously reported in juvenile dermatomyositis.

TMA has been previously reported in association with JDM, presumed secondary to TTP[4], and is a rare, but known entity in adult inflammatory myopathies. A recent case series review found 16 cases of TMA reported in adults with polymyositis or dermatomyositis and noted high complication rates and survival of only 19% in their cohort, compared with 96% and 75% of general patients with TTP and HUS, respectively. They also noted that the onset of TMA was correlated with exacerbations of the underlying myopathy[10]. Despite the limitations of terminal complement levels as diagnostic or tracking markers, it is notable that C5b-9 is upregulated in both dermatomyositis and potentially in TMA, suggesting a possible role for eculizumab therapy in the management of JDM-associated TMA. In summary, though rare, the systemic nature of vasculopathy in inflammatory myopathies creates multiple potential mechanisms for renal injury. Early recognition and management of associated conditions in setting of inflammatory myopathies may improve outcomes.

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Fig. 1. Red supernatant suggestive of hemoglobinuria or myoglobinuria (a) accompanied by muddy brown cast, many tubular epithelial cells, and few erythrocytes on microscopy (b), consistent with rhabdomyolysis.

Fig. 2.
Muscle biopsy with arrows indicating necrotic fibers