Cold Agglutinin Autoimmune Hemolytic Anemia Associated with Novel Coronavirus (COVID-19)

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Abstract:

Cold agglutinin syndrome (CAS) is a rare disorder associated with infection, autoimmune disorders, and lymphoid malignancies. We present a case of CAS associated with SARS-CoV-2 that causes COVID-19. A 46-year-old female presented with severe anemia and positive SARS-CoV-2 RNA PCR. Direct Coombs test was positive to IgG and complement. LDH was elevated and haptoglobin was undetectable. Peripheral smear revealed RBC agglutination, marked polychromasia, and many nucleated RBCs. Unfortunately, as a result of her severe hypoxemia, patient went into pulseless electrical activity before receiving transfusion and subsequently died. We postulate that CAS can be associated with COVID-19, and ongoing surveillance is required for potential association.

Introduction:
Cold agglutinin syndrome (CAS), a rare disorder accounting for 25-30% of autoimmune hemolytic anemias, has been associated with infection, autoimmune disorders and lymphoid malignancies (Jager et al. 2019). *Mycoplasma pneumoniae*, Epstein Barr virus, human immunodeficiency virus, rubella virus, Legionella, varicella-zoster virus, and influenza viruses have been commonly associated with cold agglutination (Jager et al. 2019). Described here is a case in which the patient develops acute CAS associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19).

The pathogenesis behind secondary infectious causes of CAS remains undetermined. It is clear, however, that complement activation is associated with inflammatory states, including the upregulation of pro-inflammatory cytokines (Berentsen 2020). This may indeed create the perfect storm for hemolysis, especially in such a pro-inflammatory infection as COVID-19.

A 46-year-old female with a history of immune thrombocytopenic purpura (ITP) 27 years ago during pregnancy, status post splenectomy, iron deficiency anemia, and asthma presented with muscle aches, lethargy, and dyspnea. **Blood work performed six months prior to admission revealed normal bilirubin levels and a hemoglobin of 11.7 g/dL, which was at the patient’s baseline.** Additionally, the patient had a negative rheumatologic work up in the last several years including antinuclear antibody, rheumatoid factor and anti-citrullinated protein antibody.

On admission, patient was febrile at 100.8 degrees Fahrenheit, with heart rate of 107 beats per minute, and respiratory rate of 29 breaths per minute. On examination, she was ill-appearing with generalized jaundice and increased work of breathing but did not have any evidence of petechiae or rash. Contrast computed tomography imaging showed bilateral patchy lung infiltrates without evidence of pulmonary embolism and hepatomegaly with hepatic steatosis, without lymphadenopathy.

Additional laboratory testing revealed hemoglobin of 5.3 g/dL, white blood cell count of 23,800 g/uL (75.2% neutrophils), 28.9% reticulocyte count, and normal platelets of 318,000 g/uL. Total bilirubin was elevated at 9.2 mg/dL (3.6 mg/dL direct) and a ferritin of 1930 ng/mL. Prothrombin time was normal at 24.1 seconds. Creatinine was 0.83 mg/dL with estimated glomerular filtration rate of 75.05 mL/min/1.73 square meters. SARS-CoV-2 RNA PCR was positive.
Hepatitis viral panel and a respiratory pathogen panel including *M. pneumoniae* were negative. Previous HIV 1/2 antibody testing was non-reactive.

Blood typing could not be performed due to strong cold agglutination. Direct Coombs testing with warming technique was strongly positive to IgG and complement. Lactate dehydrogenase was 1,316 u/L, and haptoglobin was undetectable. Urinalysis was 3+ positive for blood, but no red blood cells (RBC) were seen upon urine microscopy. Peripheral smear revealed agglutination of RBCs, marked polychromasia, and a large number of nucleated RBCs (Figure 1). Patient was issued urgent Type O blood given lack of blood typing. Unfortunately, within hours of admission, the patient became increasingly hypoxemic despite high flow nasal cannula at maximum settings. Moments prior to intubation, she became bradycardic and pulseless. Despite best efforts, she passed away as a result of cardiac arrest.

Increasing literature is contributing to the understanding of the COVID-19 disease process. Several other hematologic disorders have already been associated with COVID-19 including ITP and anti-phospholipid antibody syndrome (Zulfiqur 2020, Zhang 2020). While the pathophysiology of these associations has not yet been fully elucidated, the concern for a hypercoagulable state leading to cerebral infarction and venous thromboembolism in COVID-19 patients has been emphasized in many case reports (Klok et al. 2020, Zhang 2020). While several recent reports reveal both warm and cold agglutinin autoimmune hemolytic anemia as well as Evan’s syndrome with SARS-CoV-2 infection, the rapid progression and acuity presented in this case is so far unique (Lazarian et al. 2020, Li et al. 2020).

Most importantly, treatment of the underlying cause remains the mainstay of management for CAS. Finding a compatible blood transfusion via standard cross-matching can be prolonged in the presence of autoimmune hemolysis. Urgent transfusion of O negative, non-cross-matched blood raises the risk of increased hemolysis from the underlying disease process or an alloantibody present in the serum. This risk may be acceptable in an unstable patient (Swiecicki et al. 2013). Treatment of the underlying cause remains the mainstay of management for CAS. Additional treatment modalities could not be considered or instituted due to rapid deterioration of our patient and eventual demise, less than 24 hours of presenting to our institution. Our observation of this accelerated onset and progression of CAS was humbling. Ongoing surveillance will be required for further potential associations of COVID-19 and CAS.
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Black arrows represent nucleated red blood cells while green arrows represent agglutination.