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Chilling Complications: A Case of COVID-Associated Cold autoimmune Hemolytic Anemia (AIHA)

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Introduction:
Cold Agglutinin disease (CAD) also known as Cold autoimmune hemolytic anemia (AIHA) is a form of autoimmune hemolytic anemia wherein cold agglutinins (IgM autoantibodies against red blood cell (RBC) antigens) bind during cold temperatures causing clinical symptoms related to RBC agglutination resulting to hemolytic anemia. Clinicians should recognize that Cold Agglutinin disease can be secondary to an underlying pathology such as COVID-19. Here we describe an unusual case of Cold Agglutinin autoimmune Hemolytic Anemia which was diagnosed in the Emergency Department with the presence of COVID-19 and with a hospital course complicated by acute deep vein thrombosis (DVT) and bilateral pulmonary embolisms (PE’s). It was unremarkable.

Case Presentation:
A 76-year-old male presented to the emergency department for evaluation of two weeks of progressive generalized weakness, upper respiratory symptoms and several days of dark urine. He had been evaluated at an urgent care at the onset of his symptoms and was prescribed a decongestant after testing negative for COVID. He also noticed having dark colored urine for the past couple of days. He did not have any fevers, chest pain, dyspnea, nausea, vomiting, abdominal pain, night sweats, weight loss, petechia, bruising, or bleeding.

He had a past medical history of Hypertension, Type II Diabetes Mellitus, and coronary artery disease. He had not been prescribed any new medications, was not on anticoagulants and denied taking any over the counter or herbal supplements. Social history was positive for tobacco 50+ pack year, however quit 30 years ago. He denied any recent alcohol.

On presentation, his vital signs showed a blood pressure of 131/67 mm Hg, heart rate of 81 beats per minute (bpm), respiratory rate of 18 breaths per minute, temperature 97.7 degrees Fahrenheit orally, and a pulse oximetry of 97% on room air. His Body Mass Index was 39.16 kg/m². His physical exam was unremarkable with exception of mild jaundice and scleral icterus. He did not have any abdominal tenderness, rashes, petechiae, lymphadenopathy, or hepatosplenomegaly. Exam findings were unremarkable.

There was a delay with the results of the complete blood count (CBC), and the laboratory advised us that the results of the complete blood count were normal. After consultation with Hematology, we decided to obtain the complete blood count (CBC), and the laboratory advised us that the blood count was normal. Several days into his hospitalization, developed hypoxia that was disproportionate to the severity of the clinical presentation, with unexplained hyperbilirubinemia and coagulopathy in a patient with COVID-19 infection. The patient initially presented with viral symptoms, incidentally, noted to have jaundice on exam with labs notable for elevated lactate dehydrogenase (LDH), anemia, elevated creatinine, low hemoglobin, elevated LDH, and a positive Coombs test, with negative IgM, with concern for CAD-AIHA.

This case report highlights the importance of taking a comprehensive history and physical exam in patients with presumed viral illnesses and relatively benign presentation. The physical exam findings of jaundice prompted a left shift in the differential to identify the diagnosis. Cold AIHA should be considered in patients presenting with viral illnesses and laboratory evidence of hemolytic anemia and thrombocytopenia.

Pathophysiology:
Cold Autoimmune Hemolytic Anemia (AIHA) is a primarily extravascular and mediated by a complement [1]. The process involves the binding of IgM cold agglutinins to red blood cells (RBCs), followed by recruitment of components of the complement pathway. This leads to the coating of RBCs with C3b, facilitating their phagocytosis by macrophages, particularly in the liver. IgM deaglutinates from the remaining RBCs upon warming, but C3b remains attached, detectable by a positive Coombs test for complement. While complement inhibitors on RBCs usually prevent intravascular hemolysis, bystander hemolysis may lead to hemolysis in some cases [2]. Studies suggest that the severity of hemolysis in AIHA correlates with antibody properties rather than cold agglutinin titer [3,4].

Cold agglutinins are autoantibodies targeting red blood cell (RBC) antigens, primarily of the IgM isotype. While IgM or IgG cold agglutinins are rare, IgM is predominant, allowing it to bridge multiple RBCs, leading to agglutination even at low concentrations [5]. In cold agglutinin disease (CAD), these antibodies typically have kappa light chains and are polyclonal. At a time of 39°C is considered clinically significant, reflecting antibody concentration and avidity. Pathologic cold agglutinins have a thermal amplitude of 20 to 30°C or more, enabling them to be active in areas of the body where temperatures are lower [6]. Determination of specificity through serologic methods is not routinely necessary, except for transfusion management.

Prevention of Cold Autoimmune Hemolytic Anemia:
Cold Autoimmune Hemolytic Anemia typically presents in individuals under 45 and rare in older age groups, although it can occur across a wider age range. Often, individuals may not be aware of their condition until exposure to cold temperatures exacerbates symptoms. Clinical manifestations may occur in response to cold-induced immune complexes, includes urticaria, hives, urticarial vasculitis, Raynaud phenomenon, induced symptoms like acrocyanosis, livedo reticularis, and Raynaud’s phenomenon being common in colder climates. Hemolytic anemia, characterized by high lactate dehydrogenase (LDH) and hemolysis, is predictive in a median hemoglobin of around 3-9 g/dL [7]. Immunoassays are a common symptom, possibly linked to complement system activation. CAD patients may also face an increased risk of severe thromboembolism, particularly in cases of severe hemolysis. Although prophylactic anticoagulation isn’t standard practice, it may be considered during acute exacerbations or in the presence of additional risk factors.

Testing for underlying disorders:
Testing for underlying disorders is important in individuals with cold agglutinins, especially older adults and those showing evidence of infections, autoimmune, or lymphoproliferative disorders. This evaluation may include a thorough history, physical examination, and additional studies such as laboratory testing and imaging. Testing for infection, autoimmune disorders, and lymphoproliferative disorders should be considered based on clinical presentation.

Most cold agglutinins associated with infections or autoimmune disorders are likely to be polyclonal and spontaneously resolved with treatment of the underlying condition. Patients should avoid cold temperatures until recovery. In severe cases with significant hemolytic anemia, C3 deposition in membranes, and treatments targeting reticuloendothelial system (e.g., prednisolone, plasmapheresis) may be considered, especially in cases of mixed warm and cold autoimmune hemolytic anemia (AIHA). However, cold agglutinins associated with lymphoproliferative disorders may be monoclonal and do not respond to standard treatments.

Management:
The management approach to Cold Autoimmune Hemolytic Anemia involves addressing symptoms, maintaining hemoglobin levels, and managing underlying disorders if present. Treatment is indicated for symptomatic anemia, severe fatigue, or hemorrhagic complications. Cold avoidance is crucial, especially for those with chronic or severe symptoms and monoclonal cold agglutinins. Management of anemia may include transfusions or plasma exchanges for severe cases, along with therapy to reduce antibody production. Treatment decisions should be tailored to individual patient needs and medical conditions. For cases without an identifiable underlying disorder, targeting antibody production with rituximab-containing regimens may be appropriate [15].

For ambulatory patients, avoiding cold environments, including cold weather, wind, and drinks is crucial. Warm clothing should protect extremities, and individuals may need to avoid cold foods or liquids. Hospitalized patients, particularly those undergoing surgery, require special attention to maintain warmth. Intravenous solution and blood products should be warmed before use. Space heaters, blankets, and warm liquids should be provided, and fever should be managed promptly to avoid cooling blankets.

Multidisciplinary planning is necessary for hyperthermic surgical procedures to prevent acute hemolytic crisis.

Conclusions:
In conclusion, the case presented highlights the complexity and diagnostic challenges of Cold Autoimmune Hemolytic Anemia (AIHA). The patient, initially presenting with viral symptoms, was incidentally found to have jaundice on exam with labs notable for elevated lactate dehydrogenase, anemia, elevated creatinine, low hemoglobin, elevated LDH, and a positive Coombs test, with negative IgM, with concern for CAD-AIHA.

Further investigations, including flow cytometry and bone marrow biopsy, aimed to identify underlying disorders contributing to AIHA, such as lymphoproliferative disorders. Treatment involved corticosteroids, complement inhibition, and therapeutic plasma exchange (TPE) to manage acute hemolysis, along with targeting the underlying COVID-19 infection. Cold avoidance and supportive measures were also crucial in managing the patient’s condition, particularly in preventing exacerbations triggered by cold exposure. Overall, early recognition, multidisciplinary management, and tailored treatment strategies are essential in optimizing outcomes for patients with Cold AIHA.

References:
Available on request