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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 Agglutin 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).

Case Presentation:

A 74-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 anticoagulation and denied taking any over the counter or3 herbal supplements. Social history was positive for tobacco 50+ pack year, however quit 30 years ago. He denied any recent travel.

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/M^2. 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 was unremarkable.

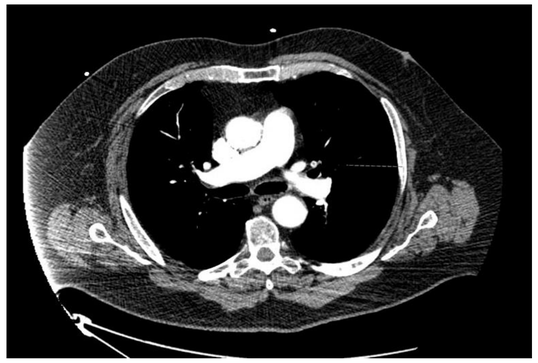
There was a delay with the results of the complete blood count (CBC), and the laboratory advised us that warming of the blood needed to be done to process it, but the initial laboratory tests that were available revealed a mild anemia (Hemoglobin at 11.9), mean corpuscular volume (MCV) 100.9, indirect hyperbilirubinemia (total bilirubin 7.9, direct bilirubin 0.9), and coagulopathy with elevated PT/PTT and INR (92.9, >120 and 2.95 respectively) without history of any former or current anticoagulant use. His COVID-19 PCR was positive. BMP was unremarkable and LFTs were normal.

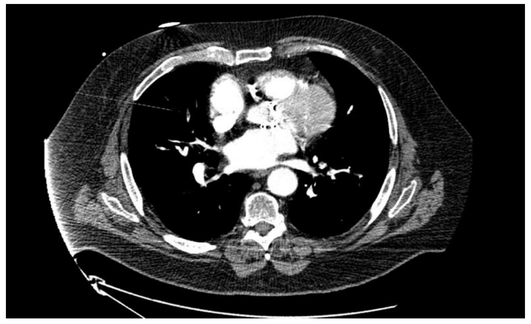
In lieu of the history & physical exam, with unexplained hyperbilirubinemia and coagulopathy in the setting of viral illness, we initiated a hemolysis work-up which revealed an elevated LDH (529), low haptoglobin (<10), elevated fibrinogen (786), and positive direct antiglobulin Coombs and DAT C3 testing. DAT IgG and EBV testing was negative.

A chest X-ray (CXR) and CT abdomen/pelvis with IV contrast were negative, except for findings consistent with bronchiolitis in the lower lung fields and incidental cholelithiasis without biliary ductal dilation. There was no evidence of malignancy. After consultation with Hematology, we initiated steroids 1mg/kg and made sure to keep the patient warm. The patient was then admitted to the stepdown/intermediate care unit.

Several days into his hospitalization, developed hypoxia that was disproportionate to the severity of his COVID-19, prompting additional imaging including CTA of his chest and lower extremity venous ultrasounds, which revealed a left femoral DVT & bilateral PEs (without heart strain), which were managed with a heparin infusion. Additional labs including peripheral flow cytometry, serum protein electrophoresis and immunofixation (SPEP+IF), serum free light chains (SFLC), mycoplasma IgM, and mixing studies were added by hematology, and were negative / not conclusive in determining the etiology of his presentation. He also underwent bone marrow biopsy which was negative for lymphoproliferative disorders.

He was transferred to the medical intensive care unit, where he was treated with five sessions of therapeutic plasma exchange, prednisone and received one of four doses of rituximab before he was discharged home on apixaban. Following this extensive work up, it was determined that COVID-19 acted as a precipitant for this case of cold autoimmune hemolytic anemia.





[Figure 1,2] CT scan, axial view, showing small filling defects in the left and right upper lobe submental and subsegmental branches.

References:

Available on request

Discussion:

The patient initially presented with viral symptoms, incidentally, noted to have jaundice on exam with labs notable for hyperbilirubinemia, anemia, elevated coagulation, low haptoglobin, elevated LDH, and a positive Coombs test, with negative IgG, with concern for Cold AIHA.

This case report highlights the importance of taking a comprehensive history and physical exam in patients with protracted viral illnesses and relatively benign presentations. The physical exam finding of jaundice prompted a lab draw, which allowed us to identify the diagnosis. Cold AIHA should be considered in patients presenting with viral illnesses and laboratory evidence of hemolysis and dysregulated coagulation.

Pathophysiology:

Cold Autoimmune Hemolytic Anemia (AIHA) is mainly extravascular and mediated by a complement [1]. The process involves the binding of IgM cold agglutinin to red blood cells (RBCs), followed by recruitment of components of the classical complement pathway. This leads to the coating of RBCs with C3b, facilitating their phagocytosis by macrophages, particularly in the liver. IgM dissociates 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, brisk hemolysis may lead to hemoglobinuria 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 IgA or IgG cold agglutinins are rare, IgM is pentameric, 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 predominantly anti-I. A titer of ≥64 is considered clinically significant, reflecting antibody concentration and avidity. Pathogenic cold agglutinins have a thermal amplitude of 28 to 30˚C or more, enabling them to be active in acral areas of the body where temperatures are lower [6]. Determination of specificity through serologic methods is not routinely necessary, except for transfusion management.

Presentation of Cold Autoimmune Hemolytic Anemia:

Cold Autoimmune Hemolytic Anemia typically presents in individuals in their mid to late 60s, although it can occur across a wide age range. Often, individuals may not be aware of their condition until exposure to cold temperatures exacerbates symptoms. Clinical manifestations persist year-round, with cold-induced symptoms like acrocyanosis, livedo reticularis, and Raynaud phenomenon being common in colder climates. Hemolytic anemia, characterized by high lactate dehydrogenase (LDH) and bilirubin levels and low haptoglobin, is prevalent, with a median hemoglobin level of around 9.5 g/dL [11.] Fatigue is a common symptom, possibly linked to complement system activation. CAD patients may also face an increased risk of venous 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 an infectious, autoimmune, or lymphoproliferative disorder. This evaluation may include a thorough history, physical examination, and additional studies such as laboratory testing and radiologic 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 can resolve spontaneously with treatment of the underlying condition. Patients should avoid cold temperatures until recovery. In severe cases with significant hemolytic anemia, close observation is necessary, and treatments targeting reticuloendothelial clearance (e.g., glucocorticoids, splenectomy) may be considered, especially in cases of mixed warm and cold autoimmune hemolytic anemia (AIHA). However, cold agglutinins associated with lymphoid malignancies or linked to a lymphoproliferative disorder are likely 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, significant fatigue, or bothersome circulatory symptoms. Cold avoidance is crucial, especially for those with chronic or severe symptoms and monoclonal cold agglutinins. Management of anemia may include transfusions or plasmapheresis for severe cases, along with therapy to reduce antibody production. Treatment decisions should be tailored to individual patient needs and underlying conditions. For cases without an identifiable underlying disorder, targeting antibody production with rituximab-containing regimens may be appropriate [13.]

For ambulatory patients, avoiding cold environments, including cold rooms, water, 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 solutions 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 hypothermic 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 and laboratory abnormalities suggestive of AIHA. Subsequent evaluation revealed indirect hyperbilirubinemia, anemia, elevated coagulation parameters, and a positive Coombs test, indicating complement-mediated hemolysis. 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 addressing 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.