

Cold hemolytic anemia: a rare complication of influenza A

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Autoimmune hemolytic anemia (AIHA) is characterized by the temperature at which the auto-antibody has the greatest avidity for the target red cell antigen, either warm or cold forms. It is detected by a positive direct antiglobulin test (DAT) also known as the direct Coombs test. DAT is used to determine if red cells have been coated in vivo with immunoglobulin, complement, or both.¹ Some causes of a positive DAT include hemolytic transfusion reactions, hemolytic disease of the fetus and newborn, AIHA, and drug-induced immune hemolysis.

Case presentation and summary

A 58-year-old woman from Brazil with past medical history only significant for cholecystectomy and cesarean section had been visiting in United States for 2 months when she presented to an outside hospital with fever, shortness of breath, and syncope that had resulted in a foot injury. She reported she had been feeling short of breath and had a nonproductive cough and malaise for about 2 weeks before presentation with sick contacts at home. On admission it was noted that she had a hemoglobin level of 7.7 g/dL (normal, 12.0-15.5 g/dL; MCV, 94 fL), total bilirubin of 2.14 mg/dL (normal, 0.2-1.0 mg/dL), and lactate dehydrogenase of 523 U/L (normal, 81-234 U/L). There were no signs of bleeding on her examination. Her DAT was positive and moderate red blood cell agglutination was reported. During the first admission at the outside hospital she was diagnosed with influenza A and completed a full course of oseltamivir (75 mg po twice daily for 5 days). A chest X-ray was negative for infiltrates and showed that the patient's lung fields were clear. She was transfused 2 units of packed red blood cells with response in hemoglobin up to 9.8 g/dL. The patient was treated with dexamethasone (4 mg IV Q8) as an inpatient and was discharged on a predni-

sone taper (40 mg, with taper by 10 mg every 3 days) with hemoglobin of 8.1 g/dL.

The patient continued to have nonproductive cough, dyspnea, fevers, chills, and generalized weakness, when she returned to the same outside hospital's emergency department 2 days after her discharge. At that time, it was noted that she had leucocytosis (white blood cell count, 34.6×10^9 per L), a hemoglobin level of 6.8 g/dL, and her total bilirubin level was 6.9 mg/dL. Her hemodynamics were unstable and she was admitted to their intensive care unit. The results of a chest X-ray revealed right lung consolidation.

The day after this admission, her hemoglobin level fell to 4.7 g/dL, and she was transfused 2 units of packed red blood cells before being transferred to our hospital. A chest X-ray at our hospital confirmed a right lung infiltrate. Vancomycin (1,250 mg IV Q12), levofloxacin (750 mg IV Q24), and maxipime (1 g IV Q12) were initiated for pneumonia and the patient was transferred to our hospital's intensive care unit. She was afebrile at 98.3°F, her pulse rate was 84 beats per minute, she was tachypneic with respiratory rate of 26 breaths per minute, her blood pressure was 98/51 mmHg, and she had an oxygen saturation of 99% on 2L oxygen via nasal cannula.

On physical examination she was noted to have scleral icterus and was in mild respiratory distress. A chest X-ray revealed a patchy opacity in the right mid to lower lung. Her initial complete blood panel revealed anemia, with hemoglobin, 6.3 g/dL; white blood cell count, 27×10^9 per L; and platelets, 533×10^9 per L. The patient was then transfused another 2 units of packed red blood cells. She was given intravenous hydration, acetaminophen, and albuterol nebulizer treatments as supportive care. She was provided with blankets to keep warm. In addition to her antibiotics, she was also given prednisone 70 mg for her respiratory symptoms.

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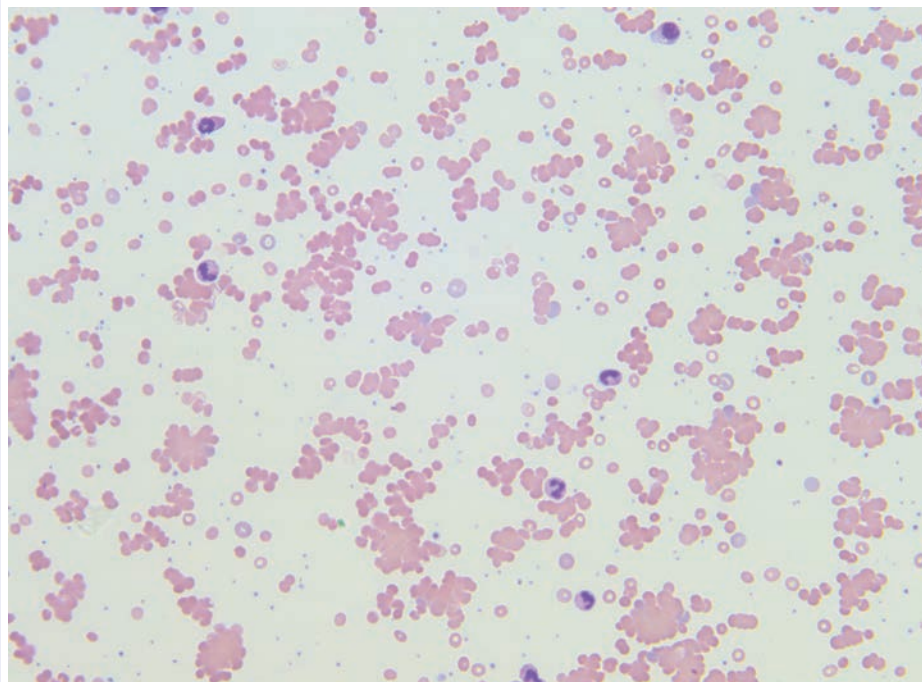


FIGURE 1 Peripheral blood smear. In cold agglutinin disease, there are prominent clumps of red blood cells. Red blood cells do not form a linear 'stack of coins' that characterize rouleaux formation, but form clumps instead. Some polychromatophilic cells are also present. (Wright's stain, 400x).

Further tests revealed haptoglobin, <30 mg/dL (normal, 36-195 mg/dL); lactate dehydrogenase, 371 U/L (normal, 98-192 U/L); and complements C3, 90 mg/dL (normal,

79-152 mg/dL) and C4, <8 mg/dL (normal, 18-55 mg/dL). Her DAT was positive, and agglutination was seen on peripheral smear (Figure 1). This was her second positive DAT as she had positive one at the outside hospital initially. Her tests for mycoplasma pneumoniae, the PCR and IgM, were negative, as were the Monospot for mononucleosis and the ANA for autoimmune disorders. Her cold agglutinin titer was 1:256 (normal, no agglutination <1:64). The patient's repeat respiratory viral panel was negative given recent full treatment for her influenza A at the previous hospital. Her blood and urine cultures were negative.

The patient was given antibiotics (vancomycin 1,250 mg IV Q12, cefepime 2 g IV Q8, and azithromycin 500 mg daily) for her pneumonia. Her respiratory status improved, and she was transferred to general medical floors after the first day of her admission. Her total bilirubin trended down to 1.9 mg/dL. She remained on prednisone 70 mg daily.

The patient remained in the hospital for an additional 6 days before being discharged home on prednisone. She wanted to return to her home country of Brazil as soon as she was able to and said she would seek outpatient follow-up there with a hematologist. At the time of her discharge, her hemoglobin was 6.6 g/dL and her reticulocyte count, 6.0%. Figures 2 and 3 illustrate her hemoglobin and reticulocyte trend during her admission at our hospital.

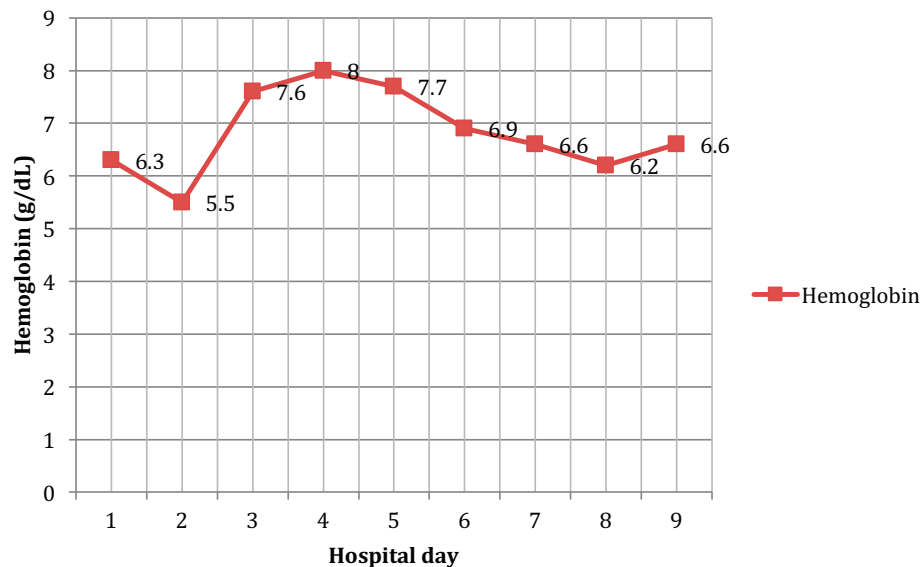


FIGURE 2 Hemoglobin level trend throughout the patient's 9-day admission. Her hemoglobin nadir was 5.5 g/dL on day 2 of admission (normal, 12-16 g/dL), and her peak was 8 g/dL on day 4.

Discussion

The incidence of cold AIHA or cold agglutinin disease (CAD) occurs about 4 per 1 million people and commonly affects women more often than men.² The cause of CAD can be subdivided into primary, idiopathic, or secondary causes, which can include infections, malignancies, or benign diseases.^{3,4} Primary CAD is a chronic disorder that is generally seen in older women. Secondary CAD can be associated with B-cell lymphoproliferative disorders, such as Waldenstrom macroglobulinemia or chronic lymphocytic leukemia, and infectious agents

such as *Mycoplasma pneumoniae* and mononucleosis caused by Epstein-Barr virus.

Mild hemolysis or acrocyanosis may occur with exposure to cold. The blood smear in CAD demonstrates red blood cell agglutination or clumping, polychromasia, and an absence of spherocytosis. In general, most cases require no treatment, but cytotoxic agents or rituximab can be used to treat more severe cases. Appropriate treatment for infectious causes of CAD includes supportive care aimed at the underlying disease process. In addition, it is helpful to keep the patient warm. There is no role for steroid therapy in CAD unlike in warm AIHA. However, our patient was symptomatic from her pneumonia, so we added steroids to help with her pulmonary insult.

The patient had a cold agglutinin titer of 1:256. Titers of 1:32 or higher are considered elevated by this technique. Elevated titers are generally rarely seen except in primary atypical pneumonia due to either *M. pneumoniae*, influenza A, influenza B, parainfluenza, and adenovirus, and in certain hemolytic anemias. Low titers of cold agglutinins have been demonstrated in malaria, peripheral vascular disease, and common respiratory diseases.

Warm AIHA is caused by IgG antibody activities at body temperature or at 98.6°F. They may or may not bind complement and are removed from circulation by the spleen. Cold AIHA is due to IgM antibodies coating red cells at lower temperatures. They bind complement and lead to red blood cell destruction of agglutinated cells. If the antibody is active at temperatures approaching 98.6°F, clinically significant intravascular and sometimes extravascular complement-mediated hemolysis occur in the liver.⁵

The incidence of warm AIHA occurs about 10 per 1 million people and affects women twice often as men.² It can be primary or idiopathic, or associated with various underlying conditions, including autoimmune disorders, immunodeficiency syndromes, lymphoproliferative disorders, other malignancies, and certain drugs. In more severe cases, jaundice and splenomegaly may occur. The blood smear in warm AIHA demonstrates variable spherocytosis, polychromasia, and rare erythrophagocytosis. Treatment usually includes steroids, cytotoxic agents, and splenectomy in severe cases.

There have been few case reports describing influenza as a cause of cold agglutinin hemolytic anemia. Chen and colleagues reported a case of influenza A infection in a

22-month-old boy.⁶ Schoindre and colleagues reported the case of a 60-year-old woman infected with influenza A H1N1 virus who died from CAD.⁷ Shizuma reported the case of a 67-year-old man with alcoholic cirrhosis who developed a mixed hemolytic anemia and was positive for influenza A.⁸

Our patient presented with influenza A, which had been diagnosed by respiratory virus panel at a different hospital, and she was anemic at the time of presentation to the outside hospital, with a positive DAT test. She was treated for influenza A with a full course of oseltamivir and then returned with complaints of worsening fatigue and was again noted to be anemic with the development of patchy opacities on chest X-ray. The patient was subsequently transferred to our hospital and remained anemic during the course of her treatment. She received supportive care for her underlying influenza A and had symptomatic improvement. She ultimately decided she would like to pursue further treatment in her native country and was discharged.

In conclusion, this case represents a rare complication of a common illness. Few cases of influenza causing hemolytic anemia have been reported in the literature. There have been reports of oseltamivir causing hemolytic anemia, but our patient presented with evidence of hemolytic anemia before initiation of the medication. In all the aforementioned cases, the patients died as a result of comorbid conditions. Our patient was stable enough to be discharged from the hospital after treatment of her comorbid conditions.

Acknowledgments

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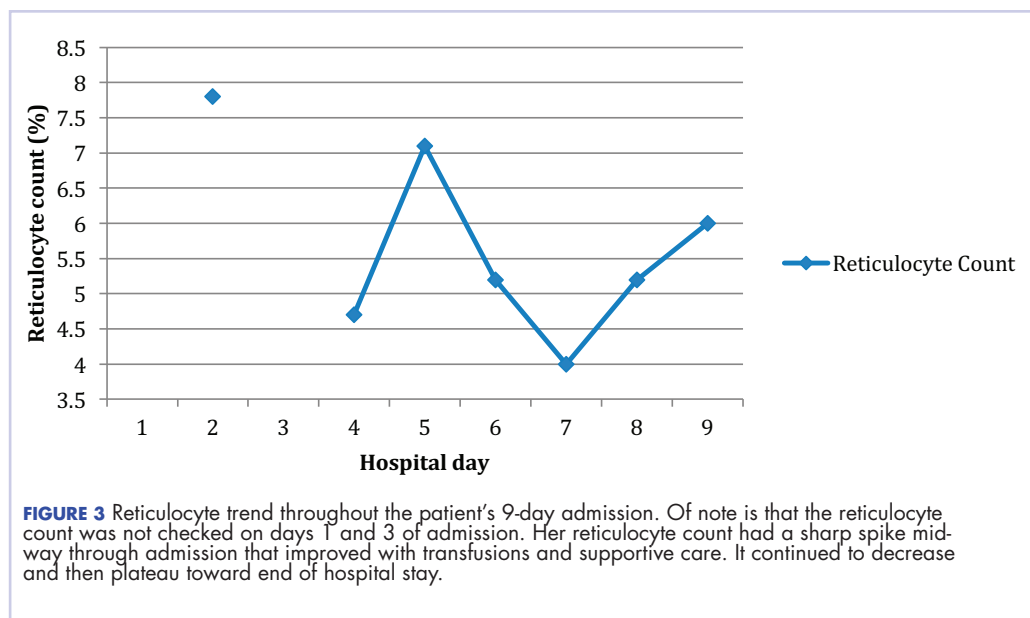


FIGURE 3 Reticulocyte trend throughout the patient's 9-day admission. Of note is that the reticulocyte count was not checked on days 1 and 3 of admission. Her reticulocyte count had a sharp spike midway through admission that improved with transfusions and supportive care. It continued to decrease and then plateau toward end of hospital stay.

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