Clinicopathological Conference

p.39  A 57-Year-Old Man Presents with Worsening Shortness of Breath and Fatigue over Ten Days

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A 57-Year-Old Man Presents with Worsening Shortness of Breath and Fatigue over Ten Days

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We present an interesting case of anemia as part of the monthly clinicopathological conference (CPC) of the University of Illinois College of Medicine. In this conference, a clinical faculty member is presented with a case of which he or she has no prior knowledge and then proceeds to describe the clinical reasoning involved in reaching a final diagnosis. This case was discussed in April 2010.

DISCUSSANTS
Chief Discussant: Ronnie Luyun MD
Pathologist: Ike Uzoaru, MD

CASE PRESENTATION
A 57-year-old male presented to the emergency department and later was admitted to the hospital for evaluation of progressively worsening fatigue and shortness of breath. The patient was in his usual state of health until 10 days prior to admission when he experienced a mild sore throat and headache which resolved spontaneously. However, since that time he noticed constant fatigue which was progressively worsening. The patient also complained of shortness of breath even on mild exertion and occasional light headedness. He reported subjective low grade night time fevers and sweats. In the three days before hospital presentation, the patient’s skin had become noticeably yellow and urine was colored brown.

On review of systems, the patient denied experiencing similar symptoms in the past. He denied chest discomfort, cough, abdominal discomfort, nausea or vomiting, change to bowel habits, and skin changes such as rashes or easy bruising. The patient was unaware of any recent sick contacts and denied travel outside the US since immigrating or any changes to medications. The remainder of a detailed review of systems was non-contributory.

Medical history was significant for gout. The patient’s only medication was allopurinol. He had immigrated to the US approximately a year before presentation. The patient was unemployed and living with his wife, who is employed as a nurse. He denied use of tobacco or alcohol.

DISCUSSION
The key features in the presentation include worsening shortness of breath, fatigue, jaundice, dark colored urine, and low grade fevers. The differential diagnosis for progressively worsening dyspnea with fatigue could be quite extensive given the underlying physiologic mechanisms responsible for it. Cardiac and respiratory disorders are the most common causes though other less common but important causes like anemia should be considered. The initial step in the evaluation of red to brown urine is centrifugation of the urine to see if color is in the urine sediment or the supernatant. In hematuria, the supernatant is clear. A red to brown supernatant that is positive for heme by dipstick is due to myoglobinuria or hemoglobinuria. Jaundice can be classified into unconjugated hyperbilirubinemia and conjugated bilirubinemia. In the event of hemoglobinuria the likely cause of jaundice would be a disorder causing unconjugated hyperbilirubinemia.

CASE PRESENTATION
The patient was afebrile on presentation. He was tachycardic (pulse 102) and tachypneic (respiratory rate 20). Blood pressure was 100/70 mmHg. Oxygen saturation was 98% breathing room air. Physical exam was significant for icterus and generalized pallor. No lymphadenopathy was appreciated. Breath sounds were clear, and no murmurs, rubs, or gales were noted on cardiac auscultation. Abdominal examination revealed an enlarged spleen palpable 4 cm below the left costal margin. No hepatomegaly was appreciated. The remainder of examination was unremarkable.
DISCUSSION
Pallor makes it likely that tachycardia and tachypnea are due to anemia. Icterus and splenomegaly certainly point to increased extravascular destruction of red blood cells.

CASE PRESENTATION
Hematological studies on admission revealed a severe normocytic anemia with hemoglobin 3.3 g/L (13–17) and hematocrit 13.5% (41–50) (mean corpuscular volume [MCV] 98.2 fl). White blood cell count was 15,500/mm³ (52% neutrophils, 7% bands, 29.7% lymphocytes, 31% monocytes). Absolute reticulocyte count was high at 5.52% (0.5–2.0) and reticulocyte index was 2.2 (1.0–2.0). Serum chemistries revealed hyponatremia (123 mM, 135–145) and hypochloremia (90 mM, 95–109). Other electrolytes and serum creatinine were unremarkable. Alkaline phosphatase, transaminases, total protein, and albumin were within their respective laboratory reference ranges. Total and direct bilirubin were elevated at 3.3 mg/dL (0.3–1.0) and 2.6 mg/dL (0.0–0.3), respectively. Coagulation studies revealed a modestly elevated international normalized ratio (INR) of 1.6 (0.9–1.3) and activated partial thromboplastin time (aPTT) of 29.6 seconds (25–35).

DISCUSSION
Agglutination of red blood cells at room temperature which resolves upon warming the slides is a strong diagnostic clue for the presence of cold agglutinins. Coombs’ test, also known as the direct antiglobulin test (DAT), is performed with the patient’s red cells washed free of adherent proteins and reacted with anti-human globulin (Coombs’ reagent). If agglutination takes place then it indicates that they are autoantibodies (usually IgG class) and/or complement present (C3d). The sample is then tested separately with reagents specific for anti-IgG and anti-C3d. The patient’s findings are confirmative of a cold agglutinin autoimmune hemolytic anemia. The next step would be to check cold agglutinin titers.

There are two major types of cold agglutinin disease, cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH). The disorders are idiopathic or secondary to another underlying disorder. Common secondary
causes include lymphoproliferative disorders, infections, and autoimmune diseases. To evaluate for potential etiologies of cold agglutinin disease several laboratory tests and imaging studies should be performed. Testing for evidence of *Mycoplasma pneumoniae*, Epstein-Barr virus (EBV), cytomegalovirus, herpes simplex virus, varicella-zoster virus, rubella virus, parvovirus, human immunodeficiency virus (HIV), and hepatitis C should be performed depending on clinical circumstances. Screening for anti-nuclear antibodies and lupus anticoagulant should be done to evaluate for autoimmune etiologies. Imaging should include plain films of the chest and/or computed tomography (CT) of the neck, chest, and abdomen to search for evidence of infection or lymphadenopathy.

Many lymphomas involve the spleen and present with splenomegaly. Diffuse large B-cell lymphoma is the most common lymphoma in adults in the US, but it does not commonly present with splenomegaly in the absence of prominent nodal and extra-nodal disease and typically produces mass lesions within the spleen rather than diffuse enlargement. Follicular and mantle cell lymphoma often present with splenomegaly, but both usually also have prominent generalized lymphadenopathy. Chronic lymphocytic leukemia or small lymphocytic lymphoma is a common indolent B-cell neoplasm in patients older than 50 years that frequently involves the spleen as well as peripheral blood and lymph nodes. Lymphoplasmacytic lymphoma typically infiltrates the bone marrow, lymph nodes, spleen and other organs and often produces an immunoglobulin M (IgM) paraprotein, a syndrome known as Waldenstrom's macroglobulinemia. Splenic marginal-zone lymphoma is a rare indolent B-cell lymphoma that most commonly involves the spleen and bone marrow. Patients typically present with splenomegaly, minimal lymphadenopathy and autoimmune hemolytic anemia.

CASE PRESENTATION

Cold agglutinin titers were significantly elevated at 1:512 dilution (< 1:32). No lymphadenopathy of the neck or chest was apparent on initial CT imaging, though splenomegaly without lymphadenopathy was eventually confirmed on a CT scan of the abdomen. Work up for infectious etiologies was negative except for increased titers of immunoglobulin G (IgG) EBV cap AB antigen (1:10,240 dilution). However, IgM antibodies were undetectable, and the elevated IgG titer was felt only to reflect prior EBV exposure. PCH was ruled out with a negative Donath Landsteiner Antibody test.

Flow cytometry immunophenotyping (FCIP) of the peripheral blood revealed a predominant population of monoclonal B-cells, lambda light chain and lymphocyte markers including CD19 and CD20. The findings on peripheral blood FCIP were confirmed by flow cytometry on a bone marrow aspirate obtained on hospital day three. (Figure 2)

The patient was admitted to the intensive care unit. He received 4 units of packed red blood cells (PRBC) hospital day one that increased his hemoglobin to 6 g/L. High dose intravenous methylprednisolone was initiated on hospital day two followed by high dose oral prednisone. On day two the patient's hemoglobin dropped to 4 g/L, and he required daily transfusions during the first five days of hospitalization due to ongoing hemolysis. Plasmapheresis was initiated on day two and continued for a total of five days. Rituximab, Danazol, and cyclophosphamide were added to the patient's treatment regimen on hospital day three, four and five, respectively. Despite plasmapheresis, immunosuppressive therapy, and daily transfusions, anemia (hemoglobin 5–6 g/L) persisted and markers of hemolysis (LDH, haptoglobin) remained abnormal consistent with a continuing hemolytic process. The patient was transferred to a tertiary care center on hospital day five.

Figure 2. A: Bone marrow aspirate under high power showing erythroid hyperplasia (pink areas) and immature lymphoid cells (blue areas). B: Bone marrow aspirate under high power demonstrating lymphocytes stained brown with immunostain CD-20.
At the tertiary care center, the patient continued to require daily PRBC transfusions. Repeat bone marrow biopsy showed pathology consistent with non-Hodgkin’s large B-cell lymphoma. Staging CT again revealed splenomegaly without lymphadenopathy. Whole body positron emission tomography (PET) imaging showed increased uptake of fluorodeoxyglucose (FDG) in the spleen and mild, diffuse increased FDG uptake in the axial skeleton. Two cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were administered, and anemia stabilized. Unfortunately, hemolytic anemia recurred shortly after hospital discharge. Splenectomy was performed during the second hospital admission, and post-operative pathology confirmed large B-cell lymphoma. After a brief remission, hemolytic anemia recurred. No etiology was identified, and the patient became transfusion dependent. He expired just four months from initial presentation and diagnosis.

**FINAL DIAGNOSIS**

Cold agglutinin autoimmune hemolytic anemia due to large B-cell lymphoma involving the bone marrow and spleen.

**DISCUSSION**

Immune hemolytic anemia (IHA) occurs when IgG and/or IgM antibodies bind to red blood cell (RBC) surface antigens and initiate RBC destruction through the complement and reticuloendothelial systems.\(^1\) Autoimmune hemolytic anemia (AIHA) is characterized by the production of auto-antibodies against RBC antigens. AIHA is a fairly uncommon disorder with an incidence of 1–3 cases per 100,000 per year.\(^1\) Classification of AIHA is presented in the Table. Depending on the patient population studied, a secondary cause of AIHA is determined in 20–80% of patients.\(^1\) Lymphoproliferative disorders are the most common secondary cause of AIHA. Other etiologies include autoimmune disorders, infections, immunodeficiency disorders, and solid tumors.

Cold hemagglutination was first reported by Landsteiner in 1903 and found to occur in humans in 1918.\(^2\) The association of cold hemagglutination with hemolysis was first described in 1937 by Rosenthal and Corten,\(^2\) and cold agglutinin hemolysis caused by monoclonal antibodies was reported in 1957.\(^3\) The term “cold” is primarily derived from immune biology as cold agglutinins bind to erythrocyte surface antigens at a temperature optimum of 0–4°C.

Cold agglutinin disease (CAD) is an extravascular immune hemolytic anemia caused by IgM class monoclonal antibodies that accounts for 16–32% of AIHA cases.\(^1\) CAD has traditionally been classified into a primary or idiopathic type and a secondary type most often associated with malignant diseases such as lymphomas.\(^2\) The prevalence of “idiopathic” primary cold AIHA is 1.6/100,000 and the incidence is 0.1/100,000/year.\(^4\) Patients with idiopathic CAD are typically middle aged or elderly. Clinical manifestations of CAD vary significantly from patient to patient depending on the thermal range of the cold antibody. Idiopathic cases are often indolent. Signs and symptoms include fatigue, dyspnea on exertion, weakness, dark urine, acrocyanosis, pallor, jaundice, hepatosplenomegaly and lymphadenopathy.\(^1\)

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<th>Table. Classification of autoimmune hemolytic anemia</th>
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<tr>
<td>Warm antibody AIHA</td>
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<tr>
<td>Idiopathic</td>
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<td>Secondary (eg, chronic lymphocytic leukemia, lymphomas, lupus)</td>
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<td>Cold antibody AIHA</td>
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<td>Cold agglutinin syndrome</td>
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<td>Idiopathic</td>
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<td>Secondary (eg, Mycoplasma pneumoniae, Epstein-Barr virus, other viral infections)</td>
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<td>Malignant disorders (eg, lymphoproliferative disorders)</td>
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<td>Paroxysmal cold hemoglobinuria</td>
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<td>Idiopathic</td>
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<tr>
<td>Secondary (viral syndromes, syphilis)</td>
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<td>Combined cold and warm AIHA (“mixed AIHA”)</td>
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<td>Drug induced immune hemolytic anemia</td>
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Autoagglutination of anticoagulated blood samples as blood cools to room temperature is characteristic and frequently the first observation made to suggest the diagnosis. Spherocytosis and anisocytosis are seen on peripheral blood smears. Bone marrow aspirates show a variable degree of erythroid hyperplasia and a slight increase of lymphoid cells. The direct antiglobulin test (DAT) is positive with anti-C3 sera but negative with anti-IgG sera. A cold agglutinin titer >1:256 dilution also helps confirm the diagnosis. 5

Most patients with idiopathic CAD experience a fairly stable mild to moderate anemia and suffer little or no disability. Though classified as a chronic hemolytic anemia without precipitating cause, recent studies have demonstrated that most idiopathic CAD patients have evidence of subclinical non-Hodgkin's lymphoma (NHL) or monoclonal gammapathy of uncertain significance (MGUS). 4 Indolent NHL progresses to diffuse large cell lymphoma in a median time of five years.

CONCLUSION

Although the occurrence of AIHA in patients with NHL is well known, little is published regarding the impact of AIHA on the clinical course of NHL patients. In a small retrospective study that included 16 patients, Sallah and colleagues found that the co-occurrence of AIHA and NHL shortened NHL survival time. 6 Based on these findings they recommended immunomodulators such as cyclosporine for treatment of patients with NHL who develop AIHA to control hemolysis as rapidly as possible. This group also recommended that AIHA be included in the risk stratification of NHL patients as an adverse prognostic factor.

Management for CAD is dependent on etiology and severity. Idiopathic CAD patients typically have mild anemia, and avoidance of cold exposure is the primary therapy. 1 However, the basis for this common recommendation is primarily anecdotal. 5 Folic acid supplementation is also recommended for these patients. 1

Treatment of secondary CAD is directed at the underlying cause. 3 The hemolysis of CAD is caused by activation of the complement system and complement-mediated phagocytosis in the liver, explaining in part why splenectomy is not effective treatment. 5 Glucocorticoids are also rarely helpful. Recognition of CAD as a clonal lymphoproliferative CD20 B-cell disorder has lead to attempts at treatment with the monoclonal anti CD-20 antibody rituximab. Several centers have reported that rituximab improves the therapeutic response to the disorder. 3 In particular, addition of rituximab to the CHOP regimen for treatment of large B-cell lymphoma complicated by CAD as in the case of this patient has been demonstrated to increase complete response rate to treatment and prolong event free survival. 1,7 Cyclophosphamide, chlorambucil, Danazol, intravenous immunoglobulin, and plasmapheresis are also used to manage cases of severe hemolysis as in this CPC case. 1,7,8

ACKNOWLEDGMENTS

The authors wish to thank Drs. Safwat Wahba and Sohail Chaudry for their care of the patient and Ms. Nancy Davis who assisted in obtaining information pertinent to the article.

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REFERENCES