Cold Agglutinin Disease: A Case Report

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Abstract
Cold agglutinin disease (CAD) is a rare type of autoimmune hemolytic anemia (AIHA) characterized by the unique property of IgM autoantibodies binding to red blood cells (RBCs) at low temperatures. Agglutination of RBCs and activation of complement are precursors to the expression of clinical features manifested as ischemic changes and hemolysis. Avoidance of cold exposure is necessary for all patients. Most patients with primary cold agglutinin disease (PCAD) will respond to anti-CD20 based therapy. Immunosuppressive agents are occasionally effective. Plasma exchange is used when rapid removal of IgM is required. In secondary cold agglutinin disease, treatment of the underlying disorder is essential. Overall prognosis in primary CAD is favorable, but variable in the presence of B-cell neoplasms. This case report is a reminder of CAD and the importance of recognizing it in clinical practice.

Introduction
Landsteiner first reported cold agglutinins in 1903; Clough described hemolysis in 1918. Schubothe suggested the term CAD in 1966. Its incidence is estimated at 1 per million, and it comprises about 15% of AIHA. Cold hemolytic syndrome can be mediated by either IgM cold agglutinins or by cold hemolysins. Anti-IgG antibodies mediate the latter group against P-antigen that can cause primary or secondary paroxysmal cold hemoglobinuria; secondary is usually associated with syphilis or children with acute viral syndrome. Cold agglutinin syndromes mediated by IgM autoantibodies can cause primary or idiopathic CAD, which is typically associated with clonal B-lymphocyte proliferation and also can be seen post-infectious or associated with malignant B-cell neoplasm. Thermal amplitude, defined as the highest temperature at which antigen-antibody interaction occurs, is regarded as more clinically significant than cold agglutinin titer. Antigens, typically I/i, on RBCs binding IgM-autoantibodies at low temperature will cause agglutination. In addition, if such binding results in fixing complement, it will progress into hemolysis. Agglutination of RBCs causes acrocyanosis, Raynaud’s phenomena, ischemia, and rarely, gangrene. Activation of the complement system can cause the destruction of RBCs and classic symptoms of anemia. We discuss a case of primary CAD and describe its clinical presentation, lab features, management, and follow-up course.

Case Presentation
A 68-year-old Caucasian female presented in February 1999 with weakness, fatigue, and shortness of breath upon exertion that occurred when exposed to cold temperatures. There was no history of recent infection, lymphoma, or pneumonia. Physical exam findings were significant for tachycardia, pallor, and peripheral cyanosis. There was no associated palpable lymphadenopathy or hepatosplenomegaly. Laboratory findings included a hemoglobin of 8.0 g/dL, mean corpuscular volume of 101 fl/cell, reticulocyte count of 9.6%, red blood cell agglutination on peripheral smear, and positive direct antiglobulin test (DAT) with complement monospecificity. Haptoglobin was less than 10 mg/dL, and lactate dehydrogenase was elevated at 378 IU/L. There was no evidence of serum monoclonal protein. Cold agglutinin titer was 1:2048. Diagnosis of primary CAD was established. She received two units of packed red blood cells due to symptomatic anemia, but no more blood transfusions since then. The patient was advised to avoid cold exposure. Her symptoms resolved. She did not require any pharmacological therapy. She did not develop any subsequent B cell neoplasm. For the past seventeen years, these preventive measures have controlled her symptoms, and she has had very mild intermittent anemia.

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Cold Agglutinin Disease is a distinct clinicopathologic entity. In contrast to warm autoantibodies, cold agglutinins bind to RBCs at or below thermal amplitude. Auto-IgM antibodies can be monoclonal such as in 90% of cases of primary CAD and B-cell neoplasm, but polyclonal in post-infectious cases. In most cases, IgM autoantibodies have anti-I specificity. They are large molecular pentamers that can simultaneously bind to many RBCs around them. In acral regions of the body, this is clinically expressed as ischemia. Laboratory findings include direct agglutination of RBCs (Figure 1), resulting in spuriously low hemoglobin, high MCH, and MCHC. These lab findings can be reversed by warming the test tube before processing. Interpretation of direct antiglobulin tests (DAT) must also be performed after warming the blood specimen to avoid incorrect interpretation. A cardinal diagnostic feature of CAD is a positive polyspecific DAT with C3d monospecificity. The risk of developing anemia and its severity are dependent on the ability of the antigen-antibody complex on RBCs to fix complement. An important step is the formation of C3b coated RBCs, most of which are removed by the liver macrophages and, to a lesser extent, removed in the spleen and by bone marrow macrophages. Surviving C3b RBCs will lead to the formation of C3d molecules, allowing detection by DAT. Further activation of the terminal components of the complement system will result in intravascular hemolysis (Figure 2).

Diagnosis of CAD must always be suspected in the anemic patient having acrocyanosis or Raynaud’s phenomenon. Such clinical findings are direct consequences of in vivo agglutination. In addition to laboratory features described above, patients will have high LDH, low haptoglobin, and hyper-indirect bilirubinemia during periods of acute hemolysis, but these laboratory values may not be significantly changed in chronic, stable patients. Diagnostic criteria are depicted in Table 1.

Management of CAD depends on the severity of symptoms, the degree of anemia, and the presence of underlying illness. In primary CAD, most patients have a chronic indolent course. Prospective data are lacking regarding how often patients can be managed...
Avoidance of cold exposure is the single most effective measure and is strongly recommended for all patients. Examples of appropriate clothing to prevent cold include warm scarves, gloves, boots, and hats. In patients with severe and recurrent symptoms, it is advised for them to relocate to a warmer geographic location. Blood bank procedures including antibody screening and compatibility testing must be done at 37 degrees to avoid false results. A blood warmer is required during blood transfusions. Communication with surgery and anesthesia groups is vital to avoid intraoperative hemolysis during procedures that involve cold environments. Corticosteroids, as single agents, are not routinely indicated. Response rates to single-agent corticosteroid therapy are about 14%, and 4 out of 5 responders were reported to have bone marrow lymphoma.\textsuperscript{20} Splenectomy has no value since the liver is the major site of extravascular hemolysis. However, if the cold reacting antibody is IgG, steroids, and splenectomy may be effective.\textsuperscript{21} When physical removal of IgM antibodies is acutely required in severe cases, plasmapheresis can be performed, but its effectiveness is transient.\textsuperscript{22} Anti-CD20 therapy represents a major advancement in the pharmacologic management of CAD. Rituximab has been studied as a single agent as well as in combination with steroids, oral Fludarabine (not available in the United States), and interferon (Table 2).\textsuperscript{20,23,24,25} Immunosuppressive agents (e.g. cyclophosphamide or chlorambucil) are used but limited by myelotoxicity.\textsuperscript{23,26} Most patients who respond to immunosuppressive agents have underlying B-cell neoplasms. Secondary causes of CAD are classified either as post-infectious or associated with monoclonal B-cell proliferation. In mycoplasma pneumonia, the frequency of hemolysis is unknown, but in one study 8% of patients had severe hemolysis.\textsuperscript{30} Cold agglutinins associated with EBV infection are specific for i-antigen. Hemolytic anemia, if present, is typically mild.\textsuperscript{31} The second major group of diseases associated with CAD is malignant disorders, in particular, B-cell neoplasms.\textsuperscript{22,33} In a large retrospective study, lymphoma was noted in 12% of patients with CAD including indolent B-cell lymphoma and diffuse large cell lymphoma.\textsuperscript{24} These patients may have either anti-i or anti-I antibodies, and

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<tr>
<th>Table 1: Essential Diagnostic Criteria For Primary Cold Agglutinin Disease\textsuperscript{19}</th>
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<tr>
<td>Hemolytic anemia</td>
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<tr>
<td>Positive polyspecific DAT with C3d monospecificity</td>
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<td>Cold agglutinin titer of at least 64 at 4 degrees C</td>
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<td>No secondary causes</td>
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<tr>
<th>Table 2: Treatment Options For Patients With CAD*</th>
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<tbody>
<tr>
<td>Number of Patients</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Rituximab Monotherapy\textsuperscript{27}</td>
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<tr>
<td>Rituximab + Interferon\textsuperscript{27}</td>
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<tr>
<td>Rituximab + PO Fludarabine\textsuperscript{28}</td>
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<tr>
<td>Low-dose Rituximab + Corticosteroids\textsuperscript{29}</td>
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*Data compiled only from prospective trials including at least 10 patients.
Case Report

A diagnosis of Cold Agglutinin Disease is important to consider in all patients with autoimmune hemolytic anemia accompanied by acrocyanosis. Cold exposure precipitates its clinical and laboratory features. Patients must be educated about avoidance of cold temperatures. In its primary form, CAD typically has a chronic benign course, but some patients will later develop B-cell neoplasms and therefore must be regularly followed. Secondary causes of CAD are more difficult to manage depending on the underlying disorder.

Conclusion

B-cell neoplasm to treatment.

References