

ASK A SPECIALIST**Ask a Pathologist**Jessica Kneib¹, Emily Coberly¹¹Department of Pathology and Anatomical Sciences, University of Missouri Health Care, Columbia, MO

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Question: After ordering a type and screen I was notified by the blood bank that my patient has cold autoantibodies. Does this mean that my patient has a cold agglutinin disease?

Answer: Many patients have antibodies in their plasma which bind to antigens present on the surface of their own red blood cells. Commonly, these autoantibodies are easily detectable in the laboratory at cold temperatures (4° C) but may be very weak or undetectable when the samples are warmed to body temperature (37° C). While cold autoantibodies are generally not clinically significant and do not cause hemolysis in the patient, they may delay serologic testing of the blood. Autoantibodies can obscure the identification of underlying clinically significant alloantibodies, requiring additional testing to find appropriate crossmatch compatible units for transfusion. Although the majority of cold autoantibodies are benign, they may rarely be associated with hemolysis.

Cold agglutinin disease (CAD) is a rare type of autoimmune hemolytic anemia caused by cold autoantibodies. The autoantibodies found in CAD differ from the commonly encountered cold autoantibodies. They are often present at an extremely high titer ($\geq 1:1000$ at 4° C) and also demonstrate a high thermal amplitude, making them easily detectable at temperatures above 30°

C. Blood samples in the laboratory may spontaneously agglutinate, and the peripheral smear shows clumps of agglutinated red blood cells (Figure 1).

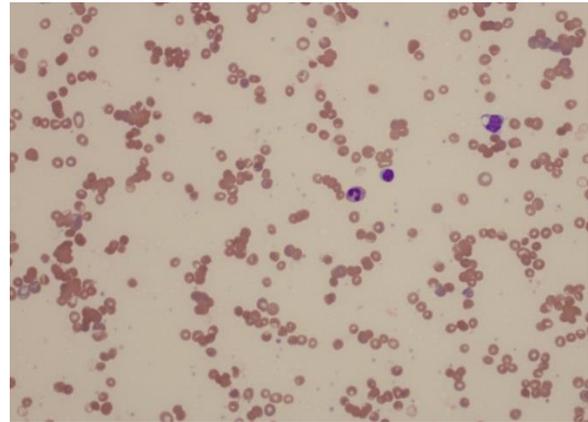


Figure 1. Peripheral smear demonstrating red blood cell agglutination due to cold agglutinin disease.

The direct antiglobulin test (DAT) is positive for complement (C3) and negative for IgG. The autoantibodies in CAD are of the IgM type and usually have specificity for the I or i carbohydrate antigens on the red blood cell surface, although autoantibody specificity alone is not diagnostic of CAD. These IgM antibodies bind to the red blood cells as they pass through lower temperatures in the peripheral circulation.

Components of complement then attach to the red blood cells before the IgM dissociates as the red blood cells return to warmer temperatures. Serologic testing in the blood bank can detect cold autoantibodies in these patients; however the presence of hemolysis must be confirmed with additional laboratory results such as hemoglobin, hematocrit, reticulocyte count, bilirubin, haptoglobin and LDH.

Patients with CAD can be divided into acute and chronic disease. The acute type occurs most often in younger patients. Hemolysis in these patients is self-limited and is often associated with infections with organisms such as *Mycoplasma pneumoniae* or the Epstein-Barr virus. Chronic CAD is typically seen in elderly patients with underlying lymphoproliferative disorders. If a transfusion is required for either acute or chronic CAD, a blood warmer must be used.

In summary, most cold autoantibodies detected in the blood bank are not clinically significant and do not point to a diagnosis of CAD. If the cold autoantibody has both a high titer and a high thermal amplitude, the patient should be evaluated for signs of hemolysis due to cold agglutinin disease.

Notes

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