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Current Developments in the Management of Hematologic Disorders

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Diagnosis and Treatment of Cold Agglutinin Disease

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H&O How common is cold agglutinin disease?

CR Cold agglutinin disease is rare, with an estimated incidence of approximately 1 per million.

H&O What causes it?

CR A population of lymphocytes in the patient's bone marrow propagates and makes an antibody that reacts against red blood cells, leading to either agglutination (clumping of red blood cells) or hemolysis (destruction of red blood cells). We do not know why this occurs, although the condition can be related to chronic lymphocytic leukemia or lymphoma. A related condition is cold agglutinin syndrome, which is a transient process that generally accompanies infections, but this is not the same as cold agglutinin disease.

H&O What are the signs and symptoms of cold agglutinin disease?

CR The signs and symptoms fall into either of 2 main categories. If the disease is related mainly to the destruction of red blood cells, it can result in anemia, fatigue, jaundice, and shortness of breath. In some cases, the urine darkens; it can take on the color of iced tea when the kidneys clear the heme released by the red blood cells.

A set of symptoms related to agglutination may also develop, in which the red blood cells clump together upon exposure to a temperature that is even slightly below core body temperature. As the blood circulates to the peripheral areas of the body, such as the fingers, toes, tip of the nose, and ears, it becomes slightly cooler. At the cooler temperature, the cold agglutinin antibodies on the surface of red blood cells cause the cells to clump together, and it becomes more difficult for them to travel through the blood vessels. Acrocyanosis then develops, in which the skin in the peripheral areas of the body turns blue or purple. If that process continues for a long period, the blood supply to the peripheral tissues is affected, and the tissues can ulcerate and die. These areas sometimes heal after the blood supply is restored, but occasionally the damage to the tissues is so great that amputation of the affected part is required, or plastic surgery with skin grafting.

Clinicians must have a high index of suspicion based on the symptoms people describe, so taking a good history is important.

H&O How is cold agglutinin disease diagnosed?

CR Cold agglutinin disease is diagnosed through laboratory testing. Clinicians must have a high index of suspicion based on the symptoms people describe, so taking a good history is important. During the physical examination, the clinician should look for signs of acrocyanosis,

and laboratory testing should include a peripheral blood cell count that includes measurement of the hemoglobin level and hematocrit to evaluate for anemia.

An important sign appears when the patient's blood is drawn because room temperature is below core body temperature, and the red blood cells clump together in the test tube. You may get a call from the laboratory telling you that your patient's blood is clotted, which it is not—the red blood cells are simply agglutinated. When that phenomenon occurs, you need to order a specialized blood bank test called a direct antiglobulin test, also known as a Coombs test. This will tell you whether antibodies are activating complement, which is what we look for on the surface of the cells. The Coombs test result will be positive for C3, which is a component of complement deposited on the surface of the red blood cells in patients with cold agglutinin disease.

H&O What special steps should be taken regarding the handling of specimens?

CR The blood must be drawn into a warmed tube and kept warm all the way to the laboratory. Otherwise, the red blood cells will stick together and become uncountable, which makes accurate measurement of the hemoglobin level and hematocrit impossible.

Another problem arises during a cold agglutinin titer test, which evaluates the quantity of antibodies in the plasma. The concentration of antibodies within the specimen varies, but if the specimen is not kept warm, the antibodies will stick together and sink to the bottom of the tube, becoming undetectable. As a result, in many cases cold agglutinin disease is not diagnosed correctly for months or even years.

If you suspect that your patient has cold agglutinin disease, ask the patient to go to a testing center where a sample can be drawn and processed immediately under warm conditions. Another possibility is referral to a tertiary care center, where everything is certain to be kept warm throughout the process. Water baths can be used to maintain the temperature of the sample at 98.6°F.

H&O How sensitive and specific is a direct Coombs test for cold agglutinin disease?

CR It is very sensitive and specific. A positive result is graded as 1+, 2+, or 3+; a small number of results in patients with a grade of 1+ are false positives, but virtually no results in those with a grade of 2+ or 3+ are false positives.

H&O How is cold agglutinin disease treated, and how effective are the treatments?

CR Immunoglobulin M (IgM) is the antibody that binds to the surface of the red blood cells in cold agglutinin disease, so therapy focuses on suppressing the production of this antibody. Reports have been published that describe the use of rituximab (Rituxan, Genentech/Biogen), a monoclonal antibody against CD20, in these patients in an effort to reduce the population of lymphocytes that may be producing the IgM. In small case series, some transient improvement in the hemoglobin level and hematocrit has occurred in 40% to 50% of patients. It often takes up to several months for that to happen, and the duration of the response tends to be short.

Some of the best data come from the studies of Dr Sigbjørn Berentsen and colleagues, but these have been single-arm trials rather than randomized, controlled trials. The investigators have used a combination of rituximab and the chemotherapy agent bendamustine (Treanda, Bendeka; Teva) in an attempt to suppress the population of lymphocytes, achieving a response rate of more than 60%. The response comes at a price, though. Chemotherapy suppresses the immune system and decreases the ability to deal with infectious complications, which is especially worrisome because patients with cold agglutinin disease tend to be older. In another trial, Dr Berentsen's group combined rituximab and the chemotherapy agent fludarabine, achieving a response rate of more than 80%. The responses appear to be fairly durable; so far, the majority of patients have remained in remission over a period of many months. Again, infectious complications and other signs of toxicity from fludarabine are a concern. So, you need to consider each patient's overall health profile before recommending one of these immunosuppressive-type chemotherapeutic regimens.

An ongoing clinical trial is looking at the possibility of using sutimlimab (formerly called BIVV009) to halt complement deposition on the surface of red blood cells, so that the cells can last in the circulation for a normal length of time. Sutimlimab exerts its effect at the very beginning of activation of the classical pathway by blocking binding of the protein complement component 1s (C1s) to complement component 1q (C1q) and complement component 1r (C1r), which must bind together to activate the next step in the pathway. Patients who are being treated with sutimlimab cannot generate any C3 via the classical pathway.

The phase 1 data on this particular compound showed a significant improvement in the hemoglobin level and hematocrit of all the patients who received this anticomplement antibody. Currently, two phase 3 trials of this agent, Cardinal (A Study to Assess the Safety and Efficacy of BIVV009 in Participants With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion; NCT03347396) and Cadenza (A Study to

Assess the Safety and Efficacy of BIVV009 in Participants With Primary Cold Agglutinin Disease Without a Recent History of Blood Transfusion; NCT03347422), are ongoing.

Administering a transfusion to these patients is challenging because the IgM antibody is present on everyone's red blood cells, not just the cells of persons who have the disease. When a patient with cold agglutinin disease receives someone else's red blood cells, the antibody also reacts with the donor's transfused red blood cells. Transfusion must be carried out carefully because the patient's body can destroy the transfused red blood cells rapidly, and clearing the byproducts of hemolysis places significant stress on the kidneys.

H&O How do the treatments for cold agglutinin disease differ from those for warm antibody autoimmune hemolytic anemia?

CR Prednisone, which is a medication commonly given to treat warm autoimmune hemolytic anemia, is not useful in cold agglutinin disease. Prednisone does not affect the production of IgM in the same way that it affects the production of IgG, which is why prednisone is not used for these patients.

Plasma exchange and splenectomy also are ineffective for cold agglutinin disease. The main difference is that hemolysis is mediated by complement in cold agglutinin disease, and by the antigen-antibody complex in warm autoimmune hemolytic anemia.

H&O What are researchers learning about the pathophysiology of the disease?

CR We are learning a lot. Although we have known for a long time that this is a complement-mediated disease, we have not had at our disposal any agent that interacts with complement effectively. It is encouraging to see that sutimlimab and other agents that address the deposition of complement on the surface of the cells are in development.

Because cold agglutinin disease is so rare, few data have been published. Doctors used to tell their patients to move to a warm climate to avoid the problems associated with their disease. Now, we understand that cold agglutinin disease is a systemic problem related to complement activity that can cause a variety of other issues.

In a study presented at the 2017 annual meeting of the American Society of Hematology (ASH), our group looked at a large population of patients in the Optum Humedica NorthStar database. We identified 814 patients with cold agglutinin disease and matched each of them—according to factors such as age, sex, and comorbidities—to 10 patients in the comparator population.

We found that the patients with cold agglutinin disease were at significantly increased risk for the development of venous and arterial thromboses, regardless of how low their hemoglobin level was. For a long time, doctors missed that fact that their patients' symptoms were caused by cold agglutinin disease—they may have assumed that the symptoms were caused by age. Now, we are looking more closely at these patients and following them over time to acquire a better understanding of what is happening inside their bodies that is related to a chronic immune process involving the antibody. For example, complement activation may be causing venous thromboembolic and arterial thromboembolic disease, which leads to the following question: What can we do to prevent that? Can we prevent it with immunotherapy, fludarabine/rituximab, or bendamustine/rituximab? Can we prevent it with anticomplement therapy? What are the long-term implications of decreasing the risk for thromboembolic disease? Does maintaining a normal hemoglobin level affect overall survival?

H&O Could you discuss the research on other complement inhibitors in cold agglutinin disease?

CR Dr Alexander Röth and colleagues published a study on the complement inhibitor eculizumab (Soliris, Alexion) in patients with cold agglutinin disease. The problem with the use of eculizumab in this disease is that 3 pathways of complement activation exist—a classical pathway, a lectin pathway, and an alternative pathway. All 3 of these pathways involve multiple steps before they converge at C5. Eculizumab is a monoclonal antibody against C5, but the problem in cold agglutinin disease is usually upstream from C5, at C3. Although eculizumab can help some patients with cold agglutinin disease, they will still have some degree of extravascular hemolysis, in which C3 remains on the surface of the red cells and the cells are cleared from the circulation in the liver. So I would say that eculizumab is helpful, but it addresses only part of the problem in cold agglutinin disease.

Another complement inhibitor that is being tested for use in cold agglutinin disease is APL-2-C3, which is in phase 2 trials. This agent is interesting because it binds to C3 and inactivates it.

H&O What are the potential risks of complement inhibitors?

CR The risks depend on the particular agent, given that each of the 3 pathways is activated by a different process. The role of complement in the body is to augment our

natural immune system—it helps our antibodies to recognize and clear pathogens from the body. By inhibiting that ability, we can make people more susceptible to certain infections. For example, we know that C5 is very important in resolving infections with certain kinds of bacteria, such as meningococcus (*Neisseria meningitidis*), so eculizumab carries a black box warning that patients taking this drug must receive meningococcal vaccine. Although sutimlimab blocks only C3, all participants in clinical trials of this agent are vaccinated against the meningococcus out of an abundance of caution. Some concern remains, however, that the immune system of someone taking a complement inhibitor might not be able to resolve an infection completely.

H&O What other advances being made in the area of cold agglutinin disease?

CR A consortium of physicians in Europe, Japan, and the United States has undertaken to produce an international registry of patients with cold agglutinin disease so that we can continue to increase our understanding of the disease. This is one of the most exciting advances in addition to the development of anticomplement therapy. We met at the most recent ASH annual meeting to determine what additional steps are needed to get this registry up and running.

Disclosure

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Suggested Readings

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