Developments in the Diagnosis and Treatment of Cold Agglutinin Disease
Speaker(s): David Kuter, MD, DPhil and Catherine Broome, MD

Dr. Kuter:
In Chapter 2, we're going to talk about developments in the diagnosis and treatment of cold agglutinin disease. Our objective here is to explain the diagnosis and management of a cold agglutinin disease to control anemia and reduce fatigue.

And I'm pleased to introduce to you Catherine Broome. Dr. Broome is Professor of Medicine in the Division of Hematology Oncology at MedStar Georgetown University in Washington, DC. And I'll begin with my first question to her. Dr. Broome, what is CAD? What is its basic pathophysiology?

Dr. Broome:
Well, thanks for having me today, Dr. Kuter. So, cold agglutinin disease is an uncommon autoimmune hemolytic anemia. It is mediated by the presence of, normally, IgM autoantibodies, although we do want to remember that occasionally, these cold agglutinins may be IgG or IgA subclass. And what happens is that the IgM recognizes an antigen on the surface of red blood cells, it binds. The binding of the IgM to this antigen, that complex, is going to activate the classical pathway of complement, and we're going to get C3 deposition on the surface of red blood cells. It's the C3 that acts as a really powerful opsonin and drives the extravascular hemolysis; that is a hallmark of cold agglutinin disease. This extravascular hemolysis is mainly taking place in the liver. Not to forget that when the IgM is bound to that red blood cell, there is also the process of agglutination, especially in acral areas where the ambient temperature may be lower than core body. And that can cause a lot of symptoms with regards to circulation in the periphery like Raynaud's phenomenon, etcetera.

Dr. Kuter:
So, my experience is that we see a lot of reports of cold agglutinins that are sent by surgeons and a wide variety of other doctors. Are all cold agglutinins the same? Or are some more potent, as those we might see in a cold agglutinin disease?

Dr. Broome:
So, we do use a titer differential to try to ascertain that this is actually a primary cold agglutinin disease. And in order to make that diagnosis, we generally like to see a titer that is greater than 1:512. Certain people may have a very low titer of cold agglutinins that either related to that very low titer or related to their thermal amplitude or avidity for the antigen are clinically insignificant.

Dr. Kuter:
So, again, to use the word thermal amplitude, I think that falls hard on someone's ears. So, what exactly does that mean?

Dr. Broome:
So, thermal amplitude is really the temperature at which the antibody is most active. And in cold agglutinin disease, there's a wide range. Some of these are only active at very low temperatures, others are relatively active closer to core body temperature. And it's those that are active closest to core body temperature that are going to tend to cause patients the most consistent difficulty.

Dr. Kuter:
So, again, we have some diagnostic issues. I think here what you've got, we have cold agglutinin disease and cold agglutinin syndrome. What's the difference between these things?

Dr. Broome:
So, primary cold agglutinin disease is going to be the presence of these IgM autoantibodies without an underlying driving condition. So, we know that there are infections such as Epstein-Barr, CMV, we know that there are lymphoproliferative disorders, CLL, Waldenstrom's that can also be associated with the production of these antibodies. And when we find a cold agglutinin, or an autoreactive IgM, in association with one of these underlying conditions, we call that cold agglutinin syndrome. And our therapy ought to be directed against the underlying condition.

When we don't find any underlying condition and we meet certain criteria, which would include the presence of this monoclonal population of B cells that we can see on the bone marrow in patients that have cold agglutinin disease, we then term primary cold agglutinin disease, and the therapy should be then directed against the primary cold agglutinin disease.

Dr. Kuter:
So, if I have a patient with a cold agglutinin report that comes back to me, what are the important aspects of the laboratory tests that should confirm the diagnosis? What do I need to do to confirm the diagnosis of cold agglutinin disease?

Dr. Broome:
Right. So, if you have seen a patient who you think has symptoms that are consistent, who comes back with a direct antiglobulin test that demonstrates C3 deposition on the surface of those red blood cells, and you have set your cold agglutinin titer, a warm specimen must be kept warm until it is processed in the laboratory, and you do come up with this titer, I think additional examinations would absolutely include evaluations for infections that we know may be associated with cold agglutinin syndrome, evaluation for underlying malignancies.

And it's really clinicians decision as to how much of that testing you do. For me personally, I think CT scan chest, abdomen, and pelvis is very important. And I also think that performing a bone marrow examination on these patients at the time of diagnosis, and probably at the time of any treatment changes, is pretty important. Because you want to evaluate that World Health Organization classification, you want to work with your pathologist, you want to do the appropriate staining, so that you can differentiate this disorder from other lymphoproliferative disorders.

Dr. Kuter:
So, if I'm going to look at my lab tests from a patient, I have Coombs test, it's positive for complement, I've got signs of hemolysis with an LDH that's elevated and a low haptoglobin, I then have a cold agglutinin titer which is of some issue, I will then do a bone marrow biopsy to show that there's probably a clonal B cell population but not enough to make a diagnosis of lymphoma. Is that how the current algorithm works?

Dr. Broome:
I think that's a very good algorithm, remembering that you also want to throw in there and make sure that you're not looking at an underlying infection.

Dr. Kuter:
And then, as you said, an additional test would be a CAT scan looking for adenopathy, hence lymphoma, a bone marrow biopsy, which I think I agree is mandatory in all these patients, and probably flow cytometry looking for clonal B cells. Is that the big list of all your evaluations?

Dr. Broome:
Absolutely.

Dr. Kuter:
Great. So, has the WHO classified this now as a unique disease? Or is it just an outlier?

Dr. Broome:
It has. So, the WHO has classified it as a low-grade lymphoproliferative disorder. It has specific markers, including MYD88 negativity that, again, you can work with your pathologist to try to differentiate this particular clone from, say, a Waldenstrom's or other low-grade lymphoproliferative clone.

Dr. Kuter:
So, we probably have skipped ahead of the game here a bit. We haven't talked much about the symptoms that patients with cold agglutinin have. But what are the things that you commonly see in patients who've got cold agglutinin disease? What are the symptoms that they present with?

Dr. Broome:
Well, as you might remember, these are an older population of patients. Generally, you're going to diagnose this in patients that are in their sixth, seventh, eighth decade of life. Many of them are coming with some nonspecific symptoms, right? Maybe a mild to moderate anemia, they are complaining about fatigue, exercise intolerance, shortness of breath, and dyspnea on exertion. You know, some of them will complain about cold-induced acrocyanotic symptoms, but some of them don't complain about the acrocyanosis. I wouldn't pin my hat on looking for acrocyanotic symptoms if you find someone who you think has a hemolytic anemia. I think doing a direct anti-globulin or Coombs test is very important.

Now, under the surface, you know, things that patients don't necessarily complain to us about or that we have only recently associated with cold agglutinin disease, include that they have an increased risk of both venous and arterial thrombotic events. They have an increased mortality when compared to age, sex, and comorbidity-matched controls. They do really report a significant impact on their quality of life. And they also have been demonstrated in a retrospective study to have increased anxiety and depression, again, when compared with an age and comorbidity-matched control population. So, this is you know, not this benign, you are a little bit anemic kind of a disease, but it really is a systemic disorder that is having significant impact on patient's quality of life.

Dr. Kuter:
Is there a staging scheme for patients as to being severe versus mild disease? Because in my practice, I've got some patients who are horribly sick from this, and other patients who have lived blindly for many decades with no troubles.

Dr. Broome:
So, there really isn't a well-established or well-evaluated staging system. We do know that patients certainly can go through periods of time when they may be relatively asymptomatic. We also know that patients can become ill very quickly with exacerbations of the hemolysis that is associated with cold agglutinin disease, particularly in association with any kind of inflammatory stress or infection.

Dr. Kuter:
So, let's switch to how you treat a patient once you've made the diagnosis. I think the first question would be: Who needs to be treated? And the second question is going to be: What are the treatment options?

Dr. Broome:
Well, who needs to be treated I think is a great question. And I think we are still learning and evaluating some of the not-very-obvious-on-laboratory-testing parameters that would gauge who needs to be treated. And I would say anyone who is symptomatic from their disease, whether they are profoundly anemic or not, whether they're requiring transfusions or not, if they have symptoms that you or they are attributing to their disease, I think thinking about treating them would be important.

When we look at how we're going to treat these patients, I think it's important to think about what aspect of the disease is most troubling for them. If the acrocyanosis is the most troubling symptom, then we really probably want to think about something that's going to be more effective at reducing the levels of IgM. And these tend to be B cell-directed therapies. There's single-agent rituximab, and then there's combinations of rituximab plus bendamustine, rituximab plus fludarabine, and then there are other B cell-directed therapies that are under investigation.

If the hemolysis and anemia is really what is the main aspect of this patient's disease, then we have anti-complement therapies. We mentioned how the hemolysis is classical complement pathway mediated, and there is a classical complement pathway inhibitor, sutimlimab, which has been approved for the treatment of patients with anemia with cold agglutinin disease. I think choosing one over the other, again,

comes down a little bit to patient preference. Some patients don't want to be on an immunosuppressive therapy, but it also I think should be, at least in part, designed to direct it against what is the main symptom that's bothering the patient.

Dr. Kuter:
So, in terms of this, we've got maybe other therapies that might be thought about as a general hematologist. Would an erythropoietic agent work in this situation just to drive more production to compensate for the destruction?

Dr. Broome:
Yeah, so, erythropoietin agents can be utilized. And certainly, in this older population, there could be some impairment to an appropriate erythropoietin response. But remember that just compensating for the hemolysis with increased erythropoietic activity doesn't necessarily deal with that complement activation. And complement activation really acts as a systemic inflammatory stimulator. So, a lot of times the fatigue is out of proportion to the degree of anemia. And then also we do believe that that complement activation, and the inflammatory nature of it, plays a role in the increased risk of thrombosis.

Dr. Kuter:
So, when it comes to treating these patients, either with sutimlimab-like drug or a chemotherapy approach, what are your major goals in treating a patient? So, what is it you want to achieve? And when do you declare it a success?

Dr. Broome:
Yeah, you know, I think for me, it's really a partnership between myself and the patient. You know, so what are the patient's goals? Generally, they want to feel better, they want to have the energy to be able to do what they would like to do. And so, those are my biggest goals.

In achieving those goals, hopefully, we have improved their anemia. And so, they are able to have a, either no evidence of hemolysis or certainly a much better compensated hemolysis. And along with that, they're going to feel better, they're going to have more energy, they're not going to be short of breath. But I think too, remembering that just giving transfusions or fixing the anemia doesn't necessarily, again, address that complement activation and that sort of systemic inflammation and all the things that go along with it.

Dr. Kuter:
Well, I think that's a very important point, because I think we tend to neglect that this is a systemic disease, not just anemia, or even just an acrocyanosis. Let me ask you one quick question in our remaining 30 seconds here, which is, we've talked about cold agglutinin disease. Cold agglutinin syndrome patients still also have active hemolysis; is there a role for any of these therapies in patients with cold agglutinin syndrome before the chemotherapy for their Waldenstrom’s, for example, kicks in?

Dr. Broome:
Yeah, I think that's a really interesting question. And I would say that there are no clinical trial data to answer that question. But there are becoming an increasing number of case reports that do suggest that anticomplement therapy can be utilized and is very effective in initially controlling sometimes that very severe hemolysis that we see while we're waiting for our therapy for the underlying condition to be effective.

Dr. Kuter:
Well, Dr. Broome, I think our time is up here. Thank you for this lovely presentation.

Dr. Broome:
Thank you.