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Case: Meet Perry Nathaniel Henry – 42-Year-Old With Anemia

Announcer:
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Dr. Broome:
Hi, my name is Dr. Catherine Broome from MedStar Georgetown University Hospital, in Washington, DC. And today we're going to discuss a case of a patient with anemia. So Perry Nathaniel Henry is a 42-year-old male who's been seen in his primary care physician's office multiple times over the past several months complaining of severe fatigue that began rather suddenly a month or so before his first visit. He's noted some dyspnea on exertion, and he's complained of intermittent, severe abdominal pain, which is not related to eating. After his third visit to the PCP, a CBC was performed that revealed a white blood cell count of 3.6, a hemoglobin of 6.2, hematocrit of 24.6, a platelet count of 147,000 with an MCV of 85.

So when we think about the evaluation of anemia, it's important to think about the quality of the anemia, which includes the severity, as well as the mean corpuscular volume. This patient has a mean corpuscular volume that falls within the normal range at 85. We would then consider evaluating the reticulocyte count. And I'll tell you that this patient had an elevated reticulocyte count of 10.5%. So we see that this patient now has a good bone marrow response to his degree of anemia. And so the considerations are, does he have intravascular hemolysis or extravascular hemolysis? And intravascular hemolysis is going to be manifested by hemoglobinuria as well as a decreased haptoglobin. And this patient happened to have both. So then we have to decide, is this an autoimmune process or is this a complement-mediated process or a microvascular process? And we're going to do that by looking at the peripheral smear.

There's no evidence of schizocytes. There's no evidence of RBC agglutination. There's no evidence of any other fracturing of cells. And we wound up with a direct antiglobulin test, which is negative. So this is not going to be an autoimmune hemolytic anemia. Therefore, we are left with evaluating the patient for the possible presence of either enzymatic deficiencies or a complement-mediated intravascular hemolysis. So this patient presented with core signs and symptoms, including intermittent abdominal pain, as well as severe fatigue and shortness of breath. So he also has evidence of homolysis, which included hemoglobinuria. He had abnormal laboratory results, which included a normocytic anemia. No evidence of thrombosis, but we want to test for homolysis. So we have evaluated the patient and he has a decreased haptoglobin, an elevated LDH, and an elevated reticulocyte count, and a negative direct antiglobulin or Coombs test. Therefore, we're going to test for PNH with a flow cytometry on the peripheral blood.

That includes a flare test. And the results are here. So when we're looking at a flow cytometry evaluation in a PNH case possibility, we want to look for some key information. Was a PNH clone detected, yes or no? And it should tell you in the first line where it says diagnosis. PNH clone identified in white blood cells and red blood cells. We always want to evaluate our clone size in white blood cells, either in granulocytes or monocytes. We can underestimate the PNH clone size if we just look at the red blood cells because they're going to be being destroyed as complement activation occurs. So in this particular patient, you can see in the graph that the monocyte clone size is about 83%. Whereas the red blood cell clone size is only about 17%.

And then we want to look at the graph, looking at the flow cytometry report, so that we can see where the abnormal cells are located.

Once we have established that this patient does have paroxysmal nocturnal hemoglobinuria by identifying in the peripheral blood a clone of white blood cells and red blood cells that have the specific abnormality that is associated with PNH, we want to think about what is going on with this patient. Now, remember that the alternative pathway of complement is sort of always constitutively active. It's always generating a certain amount of C3, which is then going to go on to generate a certain amount of C5. Normally, our CD55 and CD59 on the surface of our red blood cells are going to protect them from any intravascular hemolysis related to the generation of the membrane attack complex. But if we have abnormalities in the anchoring of these complement regulatory proteins, our red blood cells are going to be susceptible to hemolysis. And this hemolysis can be associated with pulmonary embolism, deep vein thrombosis, cardiac ischemia, and stroke. It can be associated with bone marrow failure syndromes. It can be associated with signs and symptoms of anemia, including fatigue and dyspnea.

It's associated with abdominal pain, as well as renal insufficiency, hemoglobinuria and erectile dysfunction. So when we think about this initial evaluation of our patient with newly diagnosed PNH, we can look at this table, which is provided by the Canadian PNH Network, to see what kind of testing we need to do. So we need to do a really good history and physical examination. And based on the answers to those questions that we're going to ask our patients, we need to think about a variety of testing, right? So we want to definitely be sure that we have evaluated our patient with appropriate PNH testing, flow cytometry on peripheral blood. We want to evaluate appropriately for the presence of thrombosis or symptoms that may be consistent with thrombotic disease because 40% of patients with PNH can experience a thrombotic event. We want to take a transfusion history. We want to take a medication history.

We want to know about their immune status, whether they have allergies to medications, whether they've been vaccinated. In addition, we want to think about some testing, right? So we want to evaluate our patient's bone marrow reserve. We want to look at iron stores. We want to look at erythropoietin levels. We want to think about critically evaluating organ function. So for renal function, we want to evaluate glomerular filtration rate, urinalysis, presence of microalbuminuria. We want to look at our cardiac function with a BNP, if available. And we certainly want to do a bone marrow evaluation with cytogenetics to look for coexisting aplastic anemia or myelodysplastic syndrome. We want to think about viral serologies, vitamin B12 and folate levels as well. In addition, we might want to consider an echocardiogram to evaluate any evidence of left ventricular dysfunction. We may want to consider a CT scan to evaluate asymptomatic or barely symptomatic pulmonary emboli, and/or pulmonary hypertension. We may want to do a baseline bone density and we may want to consider an ultrasound of the abdomen as well.

So thinking about guidelines for how we're going to manage our patients once we've done the thorough evaluation, remember that regardless of the clone size, a full clinical assessment is critical. PNH is confirmed if the clone size is greater than 10%. And remember, we had that monocyte clone of 83% in this patient. We talked about evaluation for evidence of thrombosis, renal function, and then clinical symptoms, the presence of abdominal pain, chest pain or dyspnea. And remember that our patient had abdominal pain and dyspnea as well as a relatively large clone size and a fairly significant anemia. So we want to think about treating our patient because they do fall in the category of high risk.

So signs and symptoms, right? Again, fatigue, abdominal pain, difficulty swallowing, erectile dysfunction, cognitive symptoms, bruising or bleeding, back pain, leg pain. These are all impacts that PNH can have on our patient's activity of daily life. And it's very important as we're monitoring and managing our patients, either on therapy or prior to the initiation of therapy, to keep a good track of what is going on with our patients so that we can intervene at the most appropriate time. What are therapies? Well, most of the therapeutic interventions that are currently available to us are C5 or C3 directed therapies. So we have monoclonal antibodies that are approved for the use in patients with paroxysmal nocturnal hemoglobinuria which include eculizumab and ravulizumab. You can see here in the blue box that there are a whole variety of others that are currently being investigated. In addition, there is one currently available C3 inhibitor, which is APL-2 or pegcetacoplan, which can be used and is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria. There are also regulator proteins and small molecule alternative pathway inhibitors that are being investigated. The idea behind the therapeutic interventions for PNH, of course, are to interrupt not only the formation of the membrane attack complex, but once you do that with C5 inhibition, you can have accumulation of C3 and you can then have deposition of C3 on the surface of red blood cells. And you can have what's called tick over, or extravascular hemolysis, once a patient is put on therapy. So we do want to monitor our patients for the possibility of that. So when our patients are on a complement inhibitor, how do we judge whether or not they are having effective therapeutic intervention?

So we want to monitor our LDH. If it is reduced, then we are thinking that this therapy is good and we can consider to monitor our patient. If CH50 has not been significantly reduced, we can consider changing our dosing interval or looking at pharmacokinetics. If the LDH remains elevated, what is the hemoglobin? If the patient is not anemic and feeling well, we might continue them on their current therapy. However, if they have symptomatic anemia, we have to assess. Do they have an adequate reticulocyte response? If not, they may be developing either bone marrow failure, folate deficiency, relative erythropoietin deficiency, or iron overload.

Do they have an elevated reticulocyte count? This may be breakthrough intravascular hemolysis. And we're back to thinking about our CH50 and whether our pharmacokinetics are good, but then we have to evaluate for extravascular hemolysis. And that might be an indication to consider switching from a C5-based therapy to a C3-based therapy. These patients could have hypersplenism, especially if they've had Budd-Chiari. They may be bleeding, if they have thrombocytopenia or dysfunctional platelets. They may have ineffective erythropoiesis as we previously discussed. So as we're treating our patients, we're almost always constantly monitoring their response to our therapy, and then potentially reacting to that by looking at dosing intervals, the amount of C5 inhibition they're receiving, or whether they might benefit from C3-based therapeutic interventions. This concludes our discussion for today. I thank you for your attention.

Announcer:
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