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Released: 12/27/2021
Valid until: 12/27/2022
Time needed to complete: 60 minutes

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# Real-World Experience in Diagnosing and Managing PNH in Special Patient Populations

Announcer:
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Dr. Weitz:
Welcome to this activity, “Real World Experience in Diagnosing and Managing PNH in Special Patient Populations.” I’m Dr. Ilene Weitz. I’m a Professor of Clinical Medicine at the Keck School of Medicine, the University of Southern California in Los Angeles.

Dr. Shammo:
And I’m Dr. Jamile Shammo, Professor of Medicine and Pathology at Rush Medical College in Chicago, and today we’re going to be giving an overview on PNH, in terms of prevalence, clinical manifestation and pathophysiology. I’m going to be discussing diagnosis and treatment of PNH within the context of patient cases, and take a brief look at ongoing clinical trials. So, Dr. Weitz, what are some of the key points about PNH that clinicians need to know?

Dr. Weitz:
Well, PNH is an extremely rare disorder. So, if clinicians haven’t seen a case, they shouldn’t be worried about that, because it is extremely rare. It is an X-linked disorder in a sense, although the effect on the X chromosome takes place after birth, so it’s not a congenital mutation. The problem with the mutation is the loss of function of the phosphatidylinositol glycan, complement class A gene, otherwise known as PIG-A. And the PIG-A gene codes for the GPI anchor – glycosylphosphatidylinisotol anchor – that acts like a little hook on the membrane of the cells. PNH is a true bone marrow disorder, so all of the cells that are generated from the bone marrow may have the PNH defect. If they don’t have the GPI anchors, they lose the capacity to link proteins that modulate the effect of complement. And so, the loss of the complement regulators that are membrane-bound, such as CD55, CD59 can result in not only hemolysis, but also can affect the platelets, lead to thrombosis the white cells, leading to inflammation.

And chronic hemolysis is the most obvious manifestation of the disease, and can be worsened by triggers such as surgery, trauma, infection and other inflammatory conditions. We know that PNH, again, is very rare. The prevalence is somewhere between one and 16 cases per million. Maybe a little underdiagnosed, because of the difficulty making the diagnosis, but it will never be a common disorder. It’s slightly more common in women than men, but the manifestations can be the same in both sexes. Most patients present in their late 20’s, early 30’s to 40’s, but you can see this in children, and you can see this in older adults as well. Dr. Shammo, what are the symptoms that might lead a patient to present to their physician, and what are the characteristics of the patients with PNH?

Dr. Shammo:
So, the clinical picture of PNH is typically dominated by intravascular hemolysis and what comes with that. So, essentially hemolytic anemia, that is DAT negative. So this is the more classic form, right, where patients present with hemolysis, their Coombs’ test is negative, they have dark urine, they have anemia, they may require transfusions, and this is in its most classical form. They may end up

having this binding of nitric oxide or nitric oxide chelation, and that can cause a vasal restriction and gives sort of the classic PNH symptoms of abdominal pain, erectile dysfunction, headaches and all of the above. So those are the paroxysms that have been described in PNH – the paroxysmal nocturnal hemoglobinuria classical form. Now there is another way to present with PNH, and that is sort of a more smoldering, indolent bone marrow failure – that situation where the disease is dominated by cytopenia, smaller PNH clone, and perhaps hemolysis may be part of the clinical picture. I've also seen patients who present with iron deficiency anemia, and had no other explanation. And only when the patient was worked up for rare conditions or rare causes of iron deficiency, was PNH identified. So, I'm curious if you have any other strange or unusual manifestations of PNH, that would prompt a physician to think about this entity.

Dr. Weitz:
Well, I think hemoglobinuria is probably the one symptom that's frequently missed. It's just assumed to be related to infection, or some other cause of bleeding from the urinary tract. And I had a patient also, who had five cystoscopies. She was told that she must have a bladder cancer, but they never found it.

Dr. Shammo.
Yeah. See? So that would be an interesting case to keep in mind. So, and you know, there are registry data on clinical characteristics of patients who have PNH, as many physicians are aware of this PNH registry, which is simply an observational study on patients – a very large number of PNH patients in this particular analysis by Schrezenmeier.

We looked at over 4,000 patients from the International PNH Registry, and we kind of wanted to look at disease activity and understand the characteristics of PNH that was reported in this patient population, and sort of associate that with the PNH clone size, and also what is known as "high disease activity," and what does that mean when you are talking about clone size. And we looked at three different compartments, if you will, relative to PNH clone. So, in this analysis, below 10% was one compartment, 10-50%, and above 50%, and then they were all evaluated according to various parameters. So what was interesting is that pretty much all patients had high disease activity, and that was defined as an LBH above 1.5, adding a symptom of PNH such as anemia or thrombotic events or abdominal pain, a higher LBH, and then you could see, obviously, I mean in the slide it's clear that the higher the PNH clone, the higher the percentage of patients that would be presenting with high disease activity. And the same thing actually repeats itself, so if you have a smaller clone size, your chances of having a bone marrow failure would be so much higher than those who would have a higher PNH clone size – over 50%, whereby your classical or hemolytic PNH would probably dominate. So that's not surprising. Similarly, if you looked at the percentage of patients who had major adverse vascular events, or included in that, thrombotic events, the higher the PNH clone size, the higher the likelihood that you would be developing thrombotic events or major adverse vascular events. But it's not to say that if your clone size is smaller, you are free from that. It still happens. Clearly, symptoms similarly can be also present with PNH clones, and as I've already alluded to, the higher the PNH clone size, the higher the likelihood that you will have hemoglobinuria, which is, to me, a very specific PNH-related symptom, as Dr. Weitz had mentioned. And the list goes on and on.

Dr. Weitz:
So, if we look at a case, you could see this 45-year-old gentleman presented to an internal medicine specialist with fatigue, abdominal pain, and bone pain. And one of the interesting things about fatigue is that it is a universal symptom in PNH. Even with small clones, fatigue is a very important part of the disease symptomatology. During the visit, he also mentioned experiencing recurrent urinary tract infections. On further discussion, it was determined that the patient reported – what he reported was episodes of dark urine, particularly during a respiratory tract infection. His medical history was positive for superficial thrombophlebitis of the left basilic vein, and he had mild renal insufficiency with an EGFR of about 50. He also had a history of a chronic macrocytic anemia. He was previously diagnosed with anemia of chronic inflammation, and received a course of steroids due to the hypothesis that his negative direct Coombs' test, or DAT – antiglobulin test – was a false negative, and that – but he didn't respond to that. So, not a typical treatment, although steroids have been used without any controlled trials in PNH. So what's typical about this presentation? The fact that he had hemoglobinuria, the fact that he had abdominal pain, which we know from the South Korean registry is probably a marker for microvascular thrombosis, and he had fatigue. And I think all of that is pretty typical, if you think about the disease.

Dr. Shammo:
But there's no doubt that because of the lack of – maybe because of the rarity of this entity, and because of the fact that there is a lot of nonspecific symptoms, the diagnostic delay has been reported on. I mean, in the literature, you see papers that say anywhere from seven to ten years. I reported on the fact that nowadays it's maybe two to five years, so maybe we're doing a little bit better. And again, it's because of the fact that we have diagnostic tests that would allow us to think about this, likely it's just a matter of trying to think about it. In fact, at least in a paper I published with a fellow of mine, some patients ended up seeing five or six physicians before someone actually thought about PNH, for that matter. Some were sent to psychiatry before someone even thought about this entity, and this was drawn from patient surveys. So, how do you overcome some of those diagnostic challenges?

Dr. Weitz:
Well, there's no question that making the diagnosis is infinitely easier and more reliable doing flow cytometry, with flare. Part of the difficulty in making the diagnosis was we used to do a test called the Ham's test, which really describes the principle of sensitivity to complement, but is impossible to do. It takes one tech all day, it's not compatible with a modern laboratory, and nobody's doing it anymore. And you could only look at red cells – you couldn't look at the white cell clones, which are much more stable and reliable. So we know that in the modern era, we can make that diagnosis on a simple, purple-top tube, and we don't even need to make it on bone marrow, and so, it's much easier. The bigger issue is that the symptoms are very nonspecific. Granted, there's a very short differential for hemoglobinuria, but nevertheless, people don't even recognize that it's hemoglobinuria and not hematuria. They're much more likely to say that it's hematuria and go in that direction.

Dr. Shammo:
And I guess the one way that we could figure that out is if someone were to bother looking at the urine analysis, and determine that there are no intact red cells, and yet there is hemoglobin in the urine sediment, right? On urine analysis. That would be extremely helpful, because if you had hemoglobin in the urine, yet no intact red cells, that's by definition hemoglobinuria.

Dr. Weitz:
Exactly, so it's really pretty easy.

Dr. Shammo:
Yes.

Dr. Weitz:
But you have to think that way, correct? (laughs) If we get back to our patient, the laboratory testing revealed that the patient had a normocytic anemia, with an increased RDW consistent with also the presence of increased reticulocytes, in – that were measured and on the smear, and concurrent iron deficiency, with a ferritin of eight nanograms per mL. The LVH was three times the upper limit of normal. There was an increase in the unconjugated bilirubin. And we confirmed that the DAT was negative. Flow cytometry showed 39% clone size for the granulocytes, 42% clone size for the monocytes, and 34% clone size of the red blood cells. The patient was then diagnosed, based on these findings, with classical hemolytic PNH. Dr. Shammo, would you like to comment on the laboratory testing?

Dr. Shammo:
So that's a sizable clone. I mean, 42% monocytes and 39% granulocytes – that's a respectable clone size. And then, of course, not surprisingly, the red cell clone size is smaller. It wouldn't be surprising. I would have expected it to be a little bit smaller, as would be typically the case, because they are destroyed by the complement, so – but they are 34%. Perhaps they were lower at some point. Maybe the patient was transfused or what have you, but – and then of course, I'm not surprised to see iron deficiency with a ferritin of eight. And high LDH – that's all goes along with iron deficiency in the setting of intravascular hemolysis and hemoglobinuria and iron loss through that, so…

Dr. Weitz:
I think it was interesting that the NCV was relatively normal, but the patient was iron deficient, which was probably masking the increased – the macrocytosis from the reticulocyte count. So that's why it was normochromic normocytic.

Dr. Shammo:
You think that there would be any credence to distinguishing the types of PNH, and do you think that we ought to think about classifying those cases accordingly?

Dr. Weitz:
Well, we know that these different types of PNH can morph from one type to the other type. We've had patients who have bone marrow failure syndromes, aplastic anemia, possibly MDS, where they have tiny, small clones that increase in size, and then the patients develop classical hemolytic PNH. We also know that classical hemolytic PNH patients can develop, or already have, a component of bone marrow failure, or bone marrow insufficiency, which is what leads them to develop more significant anemias, but they can have pancytopenia, even as part of their classical PNH presentation. They may have subclinical PNH – that's more common with aplastic anemia, but these do – these do overlap, and you can see one type morphing into the other type.

Now that we have the diagnosis confirmed in this patient, Dr. Shammo, what treatment options are there for this patient?

Dr. Shammo:
So, we have several treatment options. The very first one that was approved was eculizumab. And then later on, we have another monoclonal antibody that was approved in 2018, built on the backbone of eculizumab, known as ravulizumab, that had a longer half-life, allowing for less treatment dosing, essentially every eight weeks versus every two weeks. And, in 2021, remarkably, we had a third drug,

which is a C3 blocker, pegcetacoplan, that was also approved for the treatment of PNH. So, in a span of, what, 15 years, we managed to have three drugs approved for this very rare disease entity. So, in 2006, Professor Hillmen published the trial data describing the results of the Phase 3, double blind, placebo-controlled data evaluating the safety and efficacy of this drug compared to placebo in PNH patients, and discussing the primary endpoint which was the stabilization of the hemoglobin level and reduction of transfusion in this patient population, which was the primary endpoint. So in that trial, patients were essentially randomized to either placebo or eculizumab, and they were followed for up to 26 weeks, after which the placebo patients were allowed to cross over to the active arm. And the drug – the active drug, eculizumab – demonstrated significant stabilization of hemoglobin level, whereas 49% of those patients basically had essentially improvement with hemoglobin, and a significant reduction in the transfusion requirement, as well as improvement in their quality of life. There was – and since this is lacking the terminal complement cascade, there is an increased risk of capsulated organisms, meningococcal infections and therefore vaccination was essential, and that was a must, and teaching patients, educating them on the risks of all this was extremely important. So, the most important adverse events that were associated with this were headaches, nasopharyngitis, upper respiratory infection, but in general the drug was very well tolerated. Ravulizumab is the long-acting agent that has been studied in clinical trials, and was compared to eculizumab in two non-inferiority studies. The 301 and 302 studies compared ravulizumab to eculizumab, with both demonstrating essentially that the ravulizumab was no different than the drug, in terms of primary endpoints in the treatment-naïve being transfusion of all events as well as LDH normalization. And in the case of treatment-experienced patients, in the 302 trial, clearly here you are looking at LVH change from baseline, because clearly those patients were well-controlled on eculizumab prior to enrolling on this study. So, but what's interesting about the drug as – not only in the fact that you can give it every eight weeks – is the fact that it's also well-tolerated, so the side – safety profile of ravulizumab seems to be very similar to eculizumab, and what's interesting is to demonstrate in this drug, is that the breakthrough rate seems to be relatively lower, when compared with eculizumab, and I realize that this was not necessarily a primary nor a secondary endpoint. This was sort of an exploratory point that was investigated in the study.

So I'll discuss this one, we're talking about pegcetacoplan, and a Phase 3 trial, also known as the PEGASUS trial, which was published by the same author who talked about eculizumab, only 15 years later. And this was a Phase 3, open label nevertheless, but it compared pegcetacoplan with eculizumab. So, the 16-week data were published in the New England Journal of Medicine, demonstrating that pegcetacoplan, the novel agent, was superior to eculizumab in terms of improving the hemoglobin level from baseline, and that was actually the primary endpoint, and it was – statistically speaking, was a superiority endpoint, or I should – looked into from a superiority standpoint, whereas all other secondary points, it was a non-inferiority. And the pegcetacoplan was not inferior to eculizumab, for transfusion independence, and a reduction in reticulocyte count. Where it didn't seem to be a was in LDH reduction, as you will see in those graphs. And the drug was tolerated, but you will a different set of side effects, in terms of having the list of side effects, as you see here. So based on all the clinical trial data, how might the treating physician approach the management of the patient in the case that was presented, Dr. Weitz? Would you like to comment?

Dr. Weitz:
Sure. Well, this patient was vaccinated against Neisseria meningitidis, and regardless of the type of treatment, whether it's eculizumab or ravulizumab or pegcetacoplan, the patients would need to receive this vaccine. If – patients on pegcetacoplan needed both pneumococcus and Haemophilus vaccines as well. But in this case, the physician initiated eculizumab treatment, and then after six months, the LDH normalized which was anticipated, but the hemoglobin remained at eight grams per deciliter. The bilirubin was elevated, the indirect bilirubin was elevated, and the reticulocyte count remained increased. Now, the DAT was positive for C3d, indicating that there was – it's most likely represented extravascular clearance by – as a consequence of the C5 blockade. So some of the clinical considerations that lead to treatment selection might be the patient's response. Would there be a difference between eculizumab versus ravulizumab, in terms of extravascular clearance? Probably not, because they both work the same way. The side effect profile is relatively meager for eculizumab and ravulizumab. The main important side effect is the risk of meningococcal infection, which would be present no matter what. And with pegcetacoplan, there's a different set of side effects, particularly because this is a self-injected drug, and it's given subcutaneously by a pump. And so, a lot of the initial side effects were due to the patients' learning how to give themselves the injection and how to manage the pump, and over time, those local reactions seem to have improved. So, other things to think about – how well is the disease controlled, what's the quality of life in these patients, the risk of infections, and the risks of thrombosis in this population. Dr. Shammo, your thoughts?

Dr. Shammo:
It would require like a lot more evaluation to understand, is there a breakthrough relative to the PNH? Although the LDH seems to have normalized, is this extravascular hemolysis, and as you know, the definition of extravascular hemolysis it varies. You know, there's really no exact definition as to what that means in the literature. But it is concerning though, that the hemoglobin is still eight. There are C3 deposits, and if this patient were to be in my clinic, I would probably like to see if I could enroll them on a clinical trial, to see if maybe we would turn around their anemia, essentially.

Dr. Weitz:
Well, I think that the patient was not transfusion-dependent, but persistently anemic, and symptomatic. They were tired, and they did have some symptoms of persistent – and evidence of persistent hemolysis. The bilirubin was elevated. It was an indirect hyperbilirubinemia, the partics were high, and so the disease had sort of changed from being intravascular hemolysis to most likely extravascular clearance. And the LDH stayed normal, which is very typical for C3 clearance. It's very rare to see the LDH go up dramatically with extravascular clearance. So, in that setting, the physician felt that the patient had extravascular clearance, and might be a candidate for the pegcetacoplan, which was now available. So the patient – the physician initiated therapy with pegcetacoplan, and by eight weeks, the hemoglobin level normalized, and the patient was transfusion-independent. Let's move on to a discussion of PNH in special patients. And to begin with, we'll talk about PNH in pregnancy. What do clinicians need to be aware of in these patients?

Dr. Shammo:
Well, it's interesting, because I had several young women in my practice, and prior to having any treatment option for PNH, it would be almost unheard of to think about having these women get pregnant. In fact, many of them would tell me that they had been discouraged from becoming pregnant. And I understand that, because pregnancy in and by itself is considered a hypercoagulable state, so imagine adding PNH and then becoming pregnant on top of that. And perhaps many of them – in fact, one in particular that comes to mind, wasn't even able to get pregnant, so if – it's difficult to even get pregnant in the state of active disease. So – and those who do get pregnant, I mean, if you look at the literature, there have been multiple reports about the terrible outcome and the thrombotic events that women who got pregnant would get, and the high morbidity and mortality. So, it was very difficult. So, granted, pregnancy in and by itself increases the complement activation and could augment intravascular hemolysis and the anemia, and women who don't have PNH become anemic towards the third trimester, so therefore we can imagine hemolysis, transfusion requirement, thrombotic events and the third trimester thrombocytopenia could also get worse. So that wasn't something that women had. Having said that, I think this has changed, now that we have options for the treatment of this disease.

So – but it's also possible that PNH is first diagnosed during pregnancy. So what should prompt suspicion of PNH in patients that weren't necessarily diagnosed with this disease prior to pregnancy, Dr. Weitz?

Dr. Weitz:
I think that PNH should be suspected in pregnant women who have unexplained anemia that's disproportionate to what you would expect from them. But more importantly, if it's coupled with thrombocytopenia, if they have evidence of hemolysis, and most importantly, if they have thrombosis. And that's especially cerebral thromboses, or Budd-Chiari syndrome. I had a patient referred to me, that one of my fellows picked up. The patient was 27 weeks pregnant and presented with a cavernous sinus thrombosis, and my fellow was smart enough to look at her hemogram, and realized that she was anemic and thrombocytopenic. Sent a PNH flow, and sure enough, she had PNH. So, those are the things that would make me suspect that a pregnant woman is – might have PNH, that had previously not been diagnosed. Of those that were previously diagnosed, they do have a higher risk of complications – certainly untreated, and that's true for developing preeclampsia or HELLP syndrome, which can be very hard to diagnose and differentiate from a PNH crisis, and if they have pregnancy-associated thrombocytopenia, which could be made worse by having the PNH. Let's take a look at a patient case that may illustrate some of the difficulties during pregnancy.

Dr. Shammo:
Yes. So I have a 27-year-old woman, who initially was diagnosed with a moderately severe aplastic anemia. She had, you know, work-up for a hemoglobin of six, slightly macrocytic, her platelet count was really low, with 20,000. Her ANC was 800. Her bone marrow biopsy looked slightly hypocellular, with erythroid hyperplasia. She had complete absence of megakaryocytes, and reduction in myeloid precursors. She was tested for Fanconi, and that came back negative for chromosomal breaks with DEB. Her cytogenetic testing was normal, which was good. And none of her siblings were matched, so no stem cell transplantation was done. And she was initially treated with ATG cyclosporine, and responded beautifully. So, a few months after that, you know, everything was discontinued. So the following year, she developed a UTI, and then soon thereafter, she was presen – she presented to the emergency room with severe hemolytic crisis, and – with hemoglobinuria and went into renal failure at the time. Her LDH was as high as 4,000, and that's when PNH was suspected, because this sort of happened on the heels of an aplastic anemia. And flow cytometry of the peripheral blood was sent, and she basically had a diagnosis of PNH, with a very large granulocyte clone. So, that was her initial presentation, and essentially, she was started on eculizumab for the treatment of the disease, and she didn't really require any transfusions. She basically had hemolysis here and there, whenever she had an infection. She had a strep throat, and her hemoglobin dropped to six after that, but her hemoglobin was in the 10-11 gram range, and she just – life went on for her. She continued to have low-grade hemolysis, but essentially was okay.

We have repeated her PNH clone and size in 2013, and her clone was 97% in the granulocytes, and then she wanted to get pregnant, and that's when we decided to – and that's when she walked into my office, actually, and said that, "I am pregnant." So it wasn't like this was planned or anything else. And so, at this point, we decided to (laughs) send her to high-risk OB, and knowing the morbidity and

mortality that's associated with PNH during pregnancy, what should we do, Dr. Weitz, and what would you recommend at this point?

Dr. Weitz:
We know that there isn't any clinical trial data, and there will never be a clinical trial in pregnancy in PNH. Just too few patients, and it's very hard to do clinical trials during pregnancy. We did do an analysis of the PNH Registry, and we ended up collecting 75 pregnancies in 61 women with PNH. Now as we discussed earlier, there's a very high risk of maternal morbidity and fetal loss in these patients, without any treatment. So, it was really important to look at patients who were on treatment, and see what the outcomes were in terms of safety and efficacy, and safety and efficacy in terms of the baby's development, etc. The granulocyte clones were pretty large in these patients. Many of them had been on eculizumab prior to becoming pregnant, and what you can see is that their hemoglobins actually did very well. They were able to maintain their hemoglobins. The platelet counts actually were pretty good, and they were able to maintain their platelet counts. The granulocyte clone size was very stable. Their LDH's actually continued to be relatively normal on the treatment, and their neutrophils remained normal as well, both through the pregnancy, at delivery, and then postpartum. There was evidence of breakthrough hemolysis, occurring primarily after week 20, when there's a dilutional effect, and so the dose of eculizumab had to be increased or the frequency was increased, and that occurred in 54% of the pregnancies that progressed to delivery. The number of transfusions did increase slightly in the months prior to the delivery, but it really was not very significant. The vast majority of patients were on some form of anticoagulation, with either low-molecular-weight heparin, full dose or prophylactic dosing. It was left to the investigator to decide. And fondaparinux was used in one pregnancy. There were no thrombotic events observed during the pregnancies, and postpartum there were two episodes of sepsis, probably really not related to the eculizumab treatment, but there were two thrombotic complications that occurred, and those occurred in patients in whom the eculizumab was stopped, because they were only placed on the ecu for the pregnancy. There was premature deliveries in some cases. There was some preeclampsia noted. It was really – the fetal growth retardation was – the fetus was below the tenth percentile, but in terms of the developmental scores, the patients – the babies did very well. Most of them had a slightly prolonged stay because there were some preemies, and most of them made it to 37 weeks, which is pretty good, and they all met their developmental milestones, without exception. So eculizumab appears to be safe in pregnancy, and we really haven't had any hesitation to use it.

It originally was Category C, which meant you had to talk to your patients about the risks, and that category designation has been removed. It has no pregnancy concern category. We don't have any data on ravulizumab, so that will be interesting. I'm sure, at some point, some patient is going to get pregnant while on ravu, but we really don't have a lot of data, and there's no data on pegcetacoplan at this time. There was a patient in the PHAROAH trial that became pregnant, but she was taken off the trial. So we don't – unfortunately we don't have any data on these other therapies. Dr. Shammo, how would you have approached this patient?

Dr. Shammo:
Well, so the patient would be treated with eculizumab, and I think I would have probably increased the doses as the weight of the patient increases, and I'd probably be guided by the hemoglobin and the hemolytic parameters as well. I'd probably be mindful of vitamin and mineral deficiencies, and make sure that I address those to prevent further worsening of anemia. I'd definitely be putting the patient on prophylactic anticoagulation to prevent future thrombotic complications, given the potential risk of clots, and then involve high-risk OB to make sure that this comes to a happy ending towards the end. And essentially, at some point, obviously if the patient requires higher doses to go back to lower doses, and continue with anticoagulation six weeks postpartum. And a lot of the – my pregnant patients ultimately were treated very similarly to what was recommended in Kelly's article, and I think these recommendations were very, very important guide – provided important guidelines in an area where actually we had none for the treatment and care for patients like this.

Dr. Weitz:
Yes, I think it's actually very interesting that the patient's hemoglobin actually improved on the higher dose, which suggests that maybe she was having little episodes of pharmacologic breakthrough previous to that, so with the higher dose, she seemed to do better.

Dr. Shammo:
Yes. And actually, that was kind of an interesting observation. Higher doses of eculizumab or completely at rest via residual anemia.

Dr. Weitz:
Alright, well, we'll move on to PNH in children and adolescents. It's much less common than in adults. Of all the cases presented, about 5-10% are in adolescence, and it's estimated that the prevalence is 1.3 cases per million people per year. And the prevalence of symptoms is slightly different than what we see in the adult population. Anemia is a very prominent feature, but fatigue is also. They may have thrombocytopenia. Abdominal pain is less common, but does occur, and leukopenia occurs as well. What differences in PNH between adults and children and adolescents do clinicians need to be aware of?

Dr. Shammo:
So, I will resort, yet again, to the PNH Registry, and there was a retrospective analysis comparing the characteristics of the adult patients

with those of the pediatric population. Now the PNH prevalence in the pediatric population is really, really, very small. If it's a rare entity in the adults, it's even rarer in the pediatric group. So – but in that particular analysis, in the pediatric population, you'll find more prevalence for bone marrow failure states, and certainly less incidence of thromboembolic events than you would see in the adult population. You'll find more classic hemolytic PNH in the adults, much less so in the pediatric population. So, as a whole, you can think of it as more prevalence for sort of the bone marrow failure phenotype, severe cytopenias, smaller PNH clones in the pediatric population, and more of the larger clones, classical PNH subtype, thrombotic events in the adult patient population. And so, with that, now that we've examined some of the differences between the adult and the pediatrics, let's talk about a patient case. Dr. Weitz?

Dr. Weitz:
Alright, so we have 16-year-old female, who presented to the emergency room with disabling headache and shortness of breath. Her medical history was negative except for some asthma during early childhood. She started receiving birth control pills three months prior to the presentation in the emergency department. Her physical exam showed that she was pale, she had scleral icterus, and she was tachycardic. Her brain CT revealed thrombosis of the transfer sinus, and the patient was anticoagulated with heparin. So what things should pediatricians think about, in terms of identifying PNH patients in that population? Well, things that we should look for are whether or not they have increased dimers, their coagulation times and fibrinogen, whether they have evidence of severe anemia with evidence of increase in the LDH, whether the platelets are normal or decreased, and if the white cell count is decreased as well, presence of increased reticulocytes, negative Coombs' test, and they need to do flow cytometry. And in this case, the flow cytometry revealed an 86% granulocyte clone, monocyte clone at 80%, and the red cell clone was only 36%, which was due to the active hemolysis that the patient was experiencing. So she was diagnosed with classical PNH.

Dr. Shammo:
Yeah, I have a classical PNH with a thrombotic event, so – and a very large PNH clone, very high LDH, low hemoglobin. Fortunately, the platelets are normal, which will allow for full anticoagulation in this situation, and so the hope is that there will be no residual neurological effect from that. I mean, at least you didn't have to deal with a bone marrow failure situation, whereby you couldn't even give anticoagulation. At least in this sense, the patient would be salvaged that way, so what about…

Dr. Weitz:
I guess the question is how should we treat this patient now?

Dr. Shammo:
Yes.

Dr. Weitz:
This is 2021. Ravulizumab is approved for pediatric patients, based on a Phase 3 trial. So, they included both naïve and eculizumab-experienced patients, and they looked at the pharmacodynamics. The secondary endpoints included change in LDH from baseline, transfusion avoidance, and breakthrough hemolysis and hemoglobin stabilization, and the safety endpoints, including treatment-associated adverse events and severe adverse events. You can see that they actually did very well in terms of their levels, and in terms of the LDH improvement, and also the stabilization of the hemoglobin was very good, and very few transfusions. The treating physician discussed the treatment options with the patient and her parents. The patient was vaccinated against Neisseria meningitidis. Since she was 16, her spleen was mature, so she didn't really need to receive pneumococcal vaccination or Haemophilus influenzae vaccine. In children under the age of five, you do want to give those additional vaccines, because their spleens are not mature. After four months, her LDH was only 1.5 times the upper limit of normal. Her hemoglobin was 11.5, and although she did have two mild upper respiratory tract infections, the remainder of her symptoms were pretty mild. Dr. Shammo, do you want to talk about the treatment selection in this patient?

Dr. Shammo:
I mean I think it's obviously reasonable to begin with a long-acting C5 blocker, because it's a younger individual and it's a drug that's approved. And every eight weeks, so if need be, every two weeks treatment, and certainly if the patient has responded as well as has been described, with a hemoglobin of 11.5, there would be no reason why you wouldn't continue. It's important to kind of make sure that they are educated on risks of pneumococcal infection and make sure that they are vaccinated appropriately, and that they're educated on when to seek medical attention, and obviously for the anticoagulation piece, that they have to be counseled on bleeding risk and things of that nature. And the only other question is what to do with clone size monitoring and how often, and sort of seeing things about breakthrough hemolysis, and monitoring for other potentially devele – sort of, like the consequences of treating with C5 blockers, like the development of the extravascular hemolysis, which is a possibility, perhaps, with prolonged treatment with C5 blockers. So that would be, sort of, the long-term goal of treating a patient like that. So again, I'm an adult hematologist. I don't deal with the pediatric patients, but that would be – those would be my thoughts.

Dr. Weitz:
Right. So this is a patient who you also want to counsel. She's on birth control pills, which may have contributed to her hypercoagulability, and so she's going to need some other form of birth control, and those are things you'd have to counsel her on. But on treatment, her thrombotic risk should really decrease.

Dr. Shammo:
So I've already discussed three treatment options that we have for PNH patients that are currently available. And it is remarkable to see that we have a whole list of investigational therapies and clinical trials that are ongoing for the treatment of patients who have this entity. And you could think of them in various categories. So there's a whole slew of novel C5 blockers that are being explored, and there are also various alternate pathway blockers. There are a couple of Factor D and Factor B inhibitors that are also being explored, either as single agents or as add-on therapy to C5 blockers. And I get the benefit of those would be to see if you could put extravascular hemolysis under control. And there are many other, very interesting, smaller molecules that have different mechanisms of action, sort of silencing RNAs and the list keeps going. So, in the future we could keep looking for clinical trials that are looking to improve, not only the intravascular hemolysis and the potential thrombotic complications that could arise from this, but also to ameliorate the anemia that could originate from the extravascular hemolysis, and that could either come as a consequence of uncontrolled PNH or as a consequence of C5 blockade. So, just today, there was a paper that was published in Blood, that discussed the results of adding danicopan to eculizumab, published by investigators from the U.K. Very interesting data, and I'm sure there will be a whole lot more, coming from the American Society of Hematology meeting. So I personally look forward to more clinical trial results that will hopefully improve the outcome of patients that have this entity. Dr. Weitz?

Dr. Weitz:
I think that the most important takeaways from our talk is that number one – we have multiple options to treat patients with PNH, and considering that it's really only been 15 years to get to this point, it's really quite remarkable, and the drugs are amazingly safe, with the exception of meningococcal infections. I think that the explosion of complement inhibitors is fantastic, because it gives us the opportunity, not just to have additional therapies, but to explore how the complement system works. And I think that that's really remarkable. We know that we've changed the lives of these patients, in terms of their overall outcome. Their overall survival is approaching – is the same as the normal, healthy controls, and the fact that these patients can – women can become pregnant and deliver normal babies is really remarkable. So, over the last 15 years, the change for these patients has been dramatic and welcomed. That concludes our discussion on real-world experience in diagnosing and managing PNH in special patient populations. Thank you to Dr. Shammo for joining me today, and please be sure to complete the post-test evaluation to receive your CME credit.

Announcer:
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