The Curbsiders: Internal Medicine Podcast
Episode: *"SPEP Up Your Step"*
Audio Transcription

NORA: **Case #1:**
The first case is about Mr. Micahel Loma and he is 67 and he comes to see you in primary care for follow-up after a one-day hospital admission for community acquired pneumonia, he is feeling much better now and has finished his antibiotics. He was noted to be a little anemic during his admission, has a history of T2DM, worsening COPD over the last 2 years, he says over the past 6 months he has been a little more fatigued and has had his arthritis flaring up.

During the admission he did have an SPEP sent which is just resulted to your inbox, so he asks you what this test is and what it is sent for. So I'll throw that question over to you, Jorge!

How would you explain what an SPEP is to a patient, and what information do you look for in using it?

JORGE:
That is a very important question because it really gives us an idea of what might be happening with this patient. So, the way I am looking at this is--and I've explained it to the patient--is your body has many different types of ways of fighting infections, and one of them is creating antibodies. You have many different types of antibodies, and the way I look at it is that these are weapons that your body uses to fight infections, so if you were infected, then you bring all your weapons and you bring all your friends with all their weapons. All of the antibodies would be elevated! But in the situation where we have an SPEP that is abnormal, then we have a specific antibody that is higher than the rest. So that is not a natural state, because either you are not infected and all your antibodies should be normal limits, or you are having an infectious process and all your antibodies should be elevated across the board. The fact that only one of them is elevated and the others are not, really gives us an idea that something is not right there. What I say is different populations of cells in the patient's bodies that are producing these antibodies, and the fact that it is one of them is elevated, it means there is a population of cells that has gotten out of control and is producing these antibodies. Now, the whole other discussion to have is that increasing those antibodies is a benign or malignant increase and that takes a different discussion, but at least the initial idea is how to express these abnormal SPEP and what it means in very lay terms.

That's a great way to explain it, because this is such a common thing. Stuart, I'm sure this happens to you all the time.

STUART: Too frequently!

MATT: Because every IM patient has a slightly abnormal hemoglobin. In fact, when I'm looking at hemoglobin--especially hospitalized patients--but even in my primary care population, most people have some sort of anemia it seems.

STUART: It's weird to see a normal hemoglobin!

MATT: That's a red flag! Wait a minute, what's happening? What am I missing? Does this person have sleep apnea? Is this pseudo normal?

There are a lot of terms to define here. When we check a hepatic function panel we get a total protein. Jorge, can you talk about the 2 main fractions of protein? Because this is going to relate when we talk about the specifics of SPEP.

JORGE: I would say there are multiple different types of proteins, but 2 main types of proteins are albumin and globulin. So, I think that in general terms, I say to patients that the albumin is the nutrition protein, right? While the globulin is more like an antibody protein. So, in a patient who is normal you should have a specific level of albumin, a specific level of globulin, and that ratio, that coefficient within normal limits. Usually, the globulins are lower than the albumins; that is a typical situation. Now in patients with any type of monoclonal protein problem, either myeloma, amyloidosis, or Waldenstroms, for example, then the globulin level goes up. Now, in some patients, the albumin hasn't changed yet, but in some other patients, whether these advances have been more than the albumin also decreases. So as you can understand the ratio gets inverted, right? And the globulin gets to be higher and the albumin gets to be a little bit lower. So that will be one potential very early, easy way to understand that something is just not right with the production of antibodies. Interestingly enough, for example, a patient of mine that I saw just today, she said, "Well, my doctor saw my protein levels and she told me that I need to start taking protein shakes to increase to increase my albumin." I'm like, so this is the disease that is driving that, you know, I don't think protein shakes are going to fix it. This problem, I think we need to treat you for your disease. And that's probably going to fix the problem. You know, just to give an idea how some other people look at this, you know, with good heart, right? But from a different perspective.

MATT: To call the audience back to an episode of "The Things We Do for No Reason," Dr. Lenny Feldman was talking to us about albumin and how it's like a negative acute phase reactant. So if someone's like, inflamed or acutely ill with something, often the albumin will start to drop, and no matter how much you feed that person, often unless you reverse what's causing the low albumin, you can't get the albumin to go up. So that's albumin. I'm sure we could talk for hours about that. So, let's say for Mr. Micahel Loma, what sort of things might we get on this SPEP that was sent for him? What might that report read?

JORGE:
Yep, so the electrophoresis curve is actually a curve, you know, made out of five smaller curves. The big one, as we were talking about is albumin, that's the big one, that's the one that is going to be the highest peak, the beginning. And then you have other peaks, you have the alpha one peak, the alpha two peak, the beta peak, and then the gamma peak. And, you know, we know what the distribution of that initial for a distribution is in normal scenarios. So when we think about a monoclonal process, a monoclonal gammopathy issue, you know, typically we see a spike on the gamma region. That's the typical presentation. But the reason we call it typical is because most of the times in myeloma and other conditions, the most common protein that is affected is IgG. And IgG likes to travel into the gamma peak. And that's why we see it there. Having said that, when we see other conditions that carry more of an IgM protein, like Waldenstroms, for example, in or IgA that so myeloma can also have IgA, then those can also, you know, travel into the gamma peak, but sometimes they travel into the beta peak. So if you don't have a pathologist that is very interested in how the curves actually present, they could potentially tell you that there is no m-spike when the m-spike is actually hitting into the beta area. Very rarely we see these proteins kind of giving you false peeks into the alpha region, but has also been described much more rarely.

NORA:
Is there any good way of trying to reduce the risk of that happening, besides just trusting your pathologists? Is there a specific threshold of the beta peak above which you would say, "maybe that's actually beta plus an M-spike?"

JORGE:
Unfortunately, if you're not looking at the curves yourself, and you don't have some type of training, that's going to be very difficult. You're gonna have to trust in your pathologists, that to some degree. And at the end of the day it is the shape of it, you know? At the end of the day, what is going to give you all that. Now the issue with SPEP is they're very useful, and I'm not trying to minimize how useful they are, but they are, up to some degree, semi quantitative. They're sort of operator driven evaluations, mainly, when you have these microscopic, very tiny m-spikes. You know, I wish there is a little bit of a better test. I think we could come up with a better test, but it's a bit more difficult. I think that a better test could be an immunofixation test. The immunofixation is what gives you which type of monoclonal protein. You can have a gamma peak, but you still do not know if it's an IgG-kappa, K Kappa Kappa, or a gg kebab mix or cup alone, alone, or IGA. So, running these immunofixation, in addition to the product of races, that actually helps you understand which subtype of paraprotein that we're talking about. That can refine a little bit better the quantification of the para-protein in that specific regard. But all these techniques are still semi quantitative.

MATT:
So I want to bring this, I want to try to summarize a little bit of what you're saying here, and then bring it back to our case. And we can use Mr. Loma as the example. So we're sort of quantifying whether or not there's an M spike with the SPEP, and it's semi quantitative. And then

immunofixation - that's more of a qualitative test that tells us which type if there is an M spike, which type of protein is present there. And that could tell us if it's like, IgG or IgM, IgA, or one of the Kappa or lambda. Right? Okay. So with Mr. Loma, his tests were abnormal. He has an M spike in the gamma region. They tell us there's protein of 2.1 grams per deciliter. It's Kappa free light chain restricted. And I don't understand exactly what that means.

STUART:
Neither do I.

JORGE:
Yeah, well, that's what I'm here.

MATT:
So, this is where, you know, I'm always like, fingers crossed. When I open a SPEP that it says no m-spike detected, and then I can just like high five everyone around me. So tell us what do we do with this?

JORGE:
Yep. So these monoclonal processes - actually, let's talk about plasma cells, because these are the ones that produce immunoglobulins. And obviously, there's a clone of plasma cells but they are over producing these proteins. So these monoclonal plasma cells will produce only one type of protein. Right? In most scenarios, I would say they secrete a heavy chain...could be an IgG, IgA, or IgM. And that is almost always paired with a free light chain. But because it's a clone, it cannot produce two or three different heavy chains or the two different free light chains. So typically, you have an IgG Kappa clone, and the myeloma will be an IgG Kappa myeloma. With Waldenstrom, you have an IgM and will be either kappas or lamdas. You can have an IgM lambda Waldenstrom, right? So there's a typical way to go. So you have a heavy chain, the light chain on the side. And that's what these malignant cells produce. Having said that, very rarely, these malignant cells can produce only the free light chain protein. In that scenario, the myeloma will be kappa only malignant myeloma. In some scenarios, they have only the heavy chain without the free light chain but that'll be more rare, typically. So heavy then light chain - heavy chain and your light chain on the side.

MATT:
Right, and when you mentioned it was semi quantitative, the SPEP, they're telling us there's protein of 2.1 grams per deciliter. That's the quantitative part of it?

JORGE:
Exactly. So that result by itself is semi quantitative, because you need to assume that there's an area under the curve that is normal for everybody, which is a polyclonal globulin, and then you have the monoclonal spike on top. So you basically have to assume what the baseline is, for you to be able to estimate the spike.

MATT:

Yeah

JORGE:
So even though they're giving you 2.1 from the spike, you're still missing a little bit down there that, you know, you're assuming is polyclonal just because of the shape of it. And that's why in this scenario, sometimes we tend to ask for actual serum immunoglobulin levels, just to get a sense of what the actual level is, that's a fully quantitative process. What you lose by doing serum immunoglobulins is that you're measuring the entire scenario. So you don't know how much is polyclonal versus monoclonal, you just know that it's beyond normal or higher than normal. So I would say both values kind of complement each other. Right? They are assigned to measure the same thing, they do it up to some degree, but none of them is perfect.

MATT:
Yeah. So with polyclonal, if someone had like a rip roaring pneumonia, we were to, for some reason, get an SPEP, right. In the midst of that, we might just see all the immunoglobulin levels, like the alpha, the beta, the gamma region, it would all be up. But, if someone has some sort of a monoclonal thing going on, they're going to have more of like an actual sharp peak, like I saw church spire as a reference. And so in this case, they looked at it and he had a distinct peak. I know, there's some cut offs for these values as well. Oh, Stuart, what were you gonna say?

STUART:
I think you said that you would have immunoglobulin elevations in alpha, beta, and gamma region?

MATT:
That's different for polyclonal.

STUART:
Right, right but just bear in mind that most of the alpha and beta elevations are not immunoglobulins. That's like your acute phase reactants, your transferrin, ferritin, stuff like that.

MATT:
Okay

JORGE:
And one way of looking at this is, you can just put your hands like this, and this is essentially how the SPEP looks like. This is your albumin. This is your alpha-one, alpha-two, beta, and this is your gamma. So the gamma is typically like this kind of a mound this way, kind of a little wide. And that's when you have, for example, hepatitis, HIV or lupus or any acute infection, then you will have a wide distribution of the gamma globulins. Which is different than when you actually have a monoclonal process, in which the curve will be the same and that you have like a peak on top of it. As you say, the church spire. So the shape of it is very distinctive. And, you know, that's one way of understanding what the shape of this is.

MATT:
So for the audience at home, if you take your right...if you're driving, please don't do this...but if you take your right hand in front of you, and hold it up in front of your face, and put out your pinky finger and your thumb and bend down the three fingers in the middle. Then your pinky is the albumin. And then you have alpha-one, alpha-two, and beta. They're just smaller humps. And the gamma is your thumb, which is kind of pointed out to the side and like a nice round mound there.

JORGE:
There you go. That's a good description.

MATT:
All right. And hopefully we didn't cause any car crashes with that. But I think that's pretty. I think that's pretty cool. I think that was worth mentioning so the audience can try to look at that because I think I will remember that. All right. So what do we have? What do we tell Mr. Loma, he's got an M spike. He's freaking out. He sees he has 2.1 grams of protein. It's Kappa free light chain restricted. How would you explain that to him?

JORGE:
I think the next step would be to say: “Well, you know, there is a monoclonal process in there and we acknowledge that is not normal, right? So something is going on there.”

So the way I would say is, we need to know if this is a benign monoclonal process or a malignant monoclonal process, because there's a benign condition called monoclonal gammopathy of undetermined significance, or MGUS. If we go around, you know, just taking blood randomly from people, you will see that the rate of MGUS in the country is anywhere between 3% and 5%. Which is very prevalent, if you think about it. Having said that, that changes with age. So if you take all the 50 year olds, the rate will be probably about 1%. It'll go up to 3%, within the sixty year olds, 5% in the 70s and close to 10% within the 80s. So there's something about aging that is related to the MGUS. So there is a chance that this patient might have an actual MGUS. The thing against this being MGUS is the distribution of patient is somewhat anemic. And you can make a case that maybe the anemia is driven by this process. If the patient is hypoalbuminemic, that will even further my concern that this patient might have a malignant process. So, therefore, how do we differentiate a malignant process from a benign process? And that's where additional testing, including a bone marrow biopsy could be of help to understand better what's going on with these patients.

STUART:
So I've got the dumb primary care physician question: at what point do I not look stupid consulting hematology for this patient? At what point am I okay to hit that button?

JORGE:
I think if you have an IgG...the issue is the most common sub-type of MGUS is IgG, so you have an IgG MGUS in which the patient is completely asymptomatic, in which the patient has the

blood counts that are normal, calcium is normal, everything is fine. Your IgG is barely elevated with an M-spike, maybe less than 0.5, those patients are most likely to be benign.

Now if your M-spike is over 1.5 and there is a little bit of anemia, a little bit of hypercalcemia, then those are the patients that classically you need to refer to consultation. These days in bigger institutions, there are a number of different programs in which they are following these patients with MGUS for other research and things of that nature. So, I think if you find an MGUS in a patient, I think it's safe to refer to a hematologist, just the sole presence...I think you're better off making sure the patient does not have a malignancy and it is only a benign process. Can you be completely sure that with an M spike with 0.5 the patient does not have a small myeloma, you cannot be sure of that. Can you be sure that because the IgM is not that high that the patient does not have Waldenstroms? So you are almost always safe to--once you find an M spike--to send the patient to the hematologist.

MATT:
I think we should define asymptomatic.

JORGE:
When we think of a myeloma, for example, we all know about the hypercalcemia, renal disease, anemia, bone disease. So if patient has any of those, the patient will be considered symptomatic. If the patient does not have any of that, then the patient could be considered asymptomatic. With Waldenstroms it is more complicated, because there is not a well-defined clinical criteria. But anemia is still one of the big issues with those patients, so we do have neuropathy and hyperviscosity, the anemia is the only thing that myeloma and Waldenstroms share, but everything else, you know kidney disease is very rare in Waldenstroms, bone disease is very rare in Waldenstroms, so it's a little bit of...they are different disease they do have a neuropathy in common but really, they are clinically very different conditions. If a patient with Waldenstroms doesn't have neuropathy, not anemic, there's no evidence of hyperviscosity...then those are patients who can be considered asymptomatic. Having said all that, I think that the best person to assess the presence or absence of symptoms in somebody with myeloma or suspected Waldenstroms is a hematologist. Trust me, some hematologist sometimes have that they are confused as well. I think that in that sense, sending the patient to be seen by a specialist is reasonable--even if you felt the patient is asymptomatic. If you don't know if the patient is asymptomatic, then even more reason to send the patient to be seen.

NORA:
Are there any supplementary lab tests or procedures that you would want done before you got that referral?

JORGE:
I think what we typically do just to get a good idea of what's going on I think getting the immune fixation is key, I think getting a complete CBC and metabolic panel just to the calcium level, specifically in myeloma patient. The actual immunoglobulin levels are really important because if

you have an IgM of 1000 in Waldenstroms for example, have an IgM of 5000, those have different implications.

If you want to be fancy, you can send some free light chain levels, and lamda additionally. But I think those are the tests that we typically tend to order when we want to see what's going on with a patient. Obviously, depending on what we see, then we can order additional tests. We can order urine tests if the kidneys are suffering, additional testing for the hypercalcemia in a patient presenting with hypercalcemia, doing that complete workup is very important. PTH, intact PTH, ionized Calcium, running the TSH, Vitamin D. You are covering all the bases when the patient comes to see a hematologist.

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MATT:
So Mr. Loma, he has evidence of kidney disease, and it's been progressing. He has some mild anemia and he has an M-spike. So we're concerned for myeloma, regardless of how high the protein is here. And would you also add to the list for him the skeletal survey? And you do get all the bones? Or do you just get certain spots that are more high yield?

JORGE:
When we think about what can be done from the IM perspective I think the skeletal survey is a reasonable way to move forward. That implies XRays of skull, spine, the ribs, the hips, the long bones. Having said that, once the patient comes to see the hematologist we tend to do more specialized imaging tests. Specifically, because the skeletal survey does suffer from sensitivity. If you find a lesion, then you know something is wrong, but if you don't find a lesion, sometimes the patient might have lesions that are not detectable by skeletal survey. In that scenario, we do all the testing. MRIs, PET scans, that would be more in the realm of the heme/oncologist.

MATT:
So we're getting a skeletal survey for him and then I want to add on two other things that let's say that we sent. So I think we're going to send a urine protein electrophoresis also with immunofixation. And that needs to be a 24 hour from my understanding? Or can we do that as just like a spot urine?

JORGE:
The recommendation would be in somebody with kidney abnormalities to do a 24 hour. You have to send a couple of things. You accumulated your 24 hr urine and then you send it for protein quantification, to see if there is any excess albuminuria there. Kidney disease in myeloma usually correlates with Bence Jones proteins. So doing a 24 hour urine with albumin and electrophoresis, you can figure that out a little bit. If your albumin looks normal and there's no BJ protein, then maybe it is not a myeloma that is causing the kidney dysfunction. With diabetes you can also see some albuminuria, right? But it would be not as marked as the one that we see typically with myeloma.

NORA:

And if you could remind us what a Bence Jones protein actually is.

JORGE
The Bruce Jence protein is essentially these excess gamma globulin that we tend to see in the urine and specifically tends to be monoclonal because of these abnormalities. Now, you need to be careful with that because if you do urine electrophoresis on all the patients with gammopathies, they all are going to have a little monoclonal antibody coming out of the urine. Right? So you have to take it in the right clinical context. If you have somebody with myeloma and kidney dysfunction, then I think that is a good indication that the light chain are excess proteins are what is causing the disease.

NORA:
One more question about the UPEP, the urine electrophoresis. Would you always get it in a patient in whom you're getting an SPEP? Or do you reserve it for a kind of second line set of diagnostic tests in patients with kidney disease for example?

JORGE:
So I typically do not get it for diagnostic purposes, because I think the SPEP and the free light chains are the immunoglobulin fixation is sensitive enough to actually make a good diagnosis in understanding what's going on. But, you know, if somebody has kidney disease, then for sure, I tend to think electrophoresis in urine in the patients or if I suspect amyloidosis in those patients.

MATT:
Okay, Jorge, I think this is interesting to talk about. And we've talked about this with our great friend, "kidney boy", Joel Toph, before where the urine dipstick will test for albumin, but it doesn't necessarily pick up if there's protein like light chains. And so when you do a urine protein electrophoresis, for 24 hour urine, or if you do like a spot urine protein creatinine ratio, you could pick up somebody that has like extra globulins in their urine. Whereas you might miss that if you just did the dipstick, because of the albumin fraction. And you mentioned the the Bence-Jones protein. So you would know that from the M spike in the urine, just like there was in the serum. And then when you do the qualitative part of it with the immunofixation, it would tell you that those were - would they be the light chain portion? Or could it just be the heavy chain or light chain or both?

JORGE:
Typically, it is most commonly the free light chain component because those are smaller molecules and they can be filtered out easier by the glomeruli. But in some scenarios, the damage is much more pronounced and you can have entire heavy chain and the light chain in the urine as well.

MATT:
All right. And I think that sets up Stuart. Stuart, you had another question?

STUART:

I just wanted to ask just overall, whether or not we need to order the free light chain ratio at this point, and how we would interpret that

MATT:
Yeah, because I think how to interpret it too, because a lot of the times I'm seeing people order like SPEP, UPEP, IFV, free light chains, and then that gets dumped to me. And I'm like…

STUART
What do I do with it? I mean, it's 1.75. I mean, do I do something with that? I don't know. It's red. That's all. You know?

MATT:
This is literally why we wanted to do this show

JORGE:
I think in the right context having a free light chain is important. If you do the free light chain only, you have a free light chain only myeloma, your SPEP might actually be normal. You might not get that peak in the electrophoresis and that could be a little tricky if you think about it. You need to have the heavy chain to see that. If you have only free light chains you might be missed. That's why, just to be on the safe side, a light chain is added to the whole process, to understand it better. Now, in myeloma we looked at those proteins as a group. Then when we treat the patient we actually follow these levels of proteins to assess their response and that's where I think it's much more important--the free light chains are more important--because the IgG is going to drop to normal limits and that M spike is going to disappear and we are going to think the patient might be in a...that's where the free light chain assay comes into play. It was normal before, and is still abnormal even though the heavy chain has normalized, then the disease is not really gone. There is no stringent complement response. So for response assessment the free light chains are very very important in that specific sense. But for us to be able to quantify that for a baseline free light chain. So that's the value of having an initial free light chain. You can suspect someone has myeloma without having the free light chains, but in the case when you don't have a strong heavy chain mark, then you light chain can be the answer. You can be surprised to see that sometimes.

NORA:
And just one more question about that. Is it the absolute value that you've looked at? Or is it the ratio of Kappa to lambda?

JORGE:
That's getting more technical, but it's important as well. You want to see the absolute number in comparison to the ration. Right? Because you can have a normal kappa and a low lambda and a normal ration, that is not problematic because your kappa is normal and your lambda is normal. That is not an issue. So you need to look at the absolute number first. Right? Either the kappa or the lambda. Then your ratio does actually make sense. This becomes trickier when

you have kidney dysfunction. In kidney dysfunction, both your kappa and lambda will be elevated because of the kidney dysfunction itself. So again, everything in the right context.

MATT:
Yeah, clearly we're capable of doing that. That's what the whole show is based on. Or, hey, this, this has been a great overview of testing. And I know we're hammering you with questions. I think it's just because this causes all of us a lot of anxiety. But the good news is CBC, BMP, the SPEP, and the immunofixation, a lot of the times will get us there. And we might, as a second round of testing, do like quantitative IgG levels, like the total levels, maybe free light chains. Then depending on what we find, if there's hypercalcemia, that might send us to that workup, we might do the skeletal survey, before we send them to you. But hematology is going to really help us try to figure out what this is. And you also gave us a bunch of the symptoms to look for which were cytopenias, the calcium, the kidneys. Those were the main ones. So I think this is a great overview and framework for the audience.

NORA:
So I guess that leads into the next big question that we have, which is how you think about the different disease processes that are actually causing these abnormalities on the SPEP? And do you have a general diagnostic framework? Using clinical clues or SPEP to break it down into a nice, organized, logical step by step approach?

JORGE:
So that is the classic clinical picture of a patient with myeloma, the questions in the boards. And in those patients, you get the different levels, you understand it may be IgA/G kappa and things of that nature, and then what do you do with a patient like that?

Obviously, you need to treat those patients because the mortality in a patient with myeloma tends to be myeloma. You know about 80% of the patients with myeloma die of myeloma. And also the survival of those patients has improved actually over the last decade, and I think it's because of the newer treatments that have come along. There is a lot of research showing the plasma cells in myeloma are highly resistant to chemotherapy, they have a lot of different mechanisms that protect them against chemotherapy.

So the non-chemotherapy approach is what we are using nowadays. We're using immunomodulators, protease inhibitors, antibodies, all these with steroids and with that, you know, we have, I would say myeloma is one of the conditions in which there have been more FDA approvals in the last decade than any other hematologic malignancy for that MATTer. And that's a lot to say because in lymphoma we have had a lot of developments as well. So I think the overall survival of patients have changed in my lifetime, actually in my lifetime as a hematologist.

When I was a fellow, the median overall survival of myeloma was 3 years. The median overall survival now is about 8 years on these patients. That sounds like a lot if you are a myeloma patient, obviously. But in the whole realm of things, it is a massive improvement on the patient's

survival. Now we have about 30-40% of patients might be alive longer than 10 years, which when I was training, that was an impossible thing to think about. So I think the research is important to understand how we can treat those patients. Now, Waldenstrom's is a little bit different. Waldenstrom's is a lymphoma, a lymphoplasmacytic lymphoma in which a component of the disease is a plasma cell dyscrasia. But the main stem cell of malignancy is not the plasma cell, so these patients with lymphoplasmacytic lymphoma tend to have IgM hypersecretion. You can also see a little bit of IgG and IgA, but that is for a different lecture.

But the classic is this IgM secretion, and these patients tend to present different than myeloma patients. I think they share the anemia as we were saying earlier, but the IgM has its own physical chemical properties on its own. It's a pentamer, it is a larger molecule compared to IgG/IgA. And these patients can present with hyperviscosity, that's a classic manifestation of Waldenstrom's. Nosebleeds, blurred vision because of retinal hemorrhages, headaches…IgM is typically in the 4 5 6 thousand levels mL per deciliter, and that is one presentation of patients with Waldenstrom's.

The other one is neuropathy, about 20% of patients can have this neuropathy, typically sensory, bilateral, distal, meaning it starts in the toes and then progresses proximally very slowly usually over months to years. These patients can have antibodies, you know 50% of the time they have demyelination in nerve conduction studies, and then you have the anemia which is classic presentation of these patients. How frequent we see kidney dysfunction because of Waldenstrom's, 2-3% of the cases. So it is much lower than in myeloma which is 40-50% of cases will have kidney problems. How many patients with Waldenstrom's have actually lytic lesions in the bone? Less than 1%, very unlikely compared to myeloma which is 30-40% of patients will have some lytic lesions at some point. So the management of these conditions are very different. Finally, the survival of patients with Waldenstrom's is actually better than the patients with myeloma. Number 1, the mortality because of Waldenstrom's is anywhere between 10 and 20%, so 4 out of 5 patients will not die because of Waldenstrom's, they will die because of other reasons. And the median survival of these patients is anywhere around 15 years, easily double in average than myeloma. And the treatments are a little bit similar because we have borrowed a lot of treatments from myeloma, we have borrowed a lot of treatments from lymphoma. So we use a little more chemotherapy in this condition, these cells are actually more sensitive to chemotherapy than plasma cells are. But we use some of the treatments from myeloma like protease inhibitors, we use antibodies, and we have a new family of medications called BTK inhibitors that are oral agents, so the overall survival of patients with Waldenstrom's have actually increased over the last decade with the newer treatments, but the ground gain is much more substantial for myeloma as you can understand when the outcomes are still not as good as, but the ground coverage is much more than for Waldenstrom's. We are working on that as well. Now, amyloidosis tends to be the toughest one out of the 3. I think the mortality around amyloidosis not only is more pronounced but is also shorter, mainly when you have cardiac amyloidosis. Amyloidosis is the type of disease that if you find it in the fat pad biopsy, cardiac biopsy, or the kidney biopsy, then you know the patient has it, but if you suspect clinically the patient has this disease and you can not find it, you're still not sure the patient doesn't have it.

MATT: That's reassuring.

JORGE:
I know. Trust me, welcome to my life.

So this is the toughest part. Amyloidosis can be suspected in many different situations. And the classic situation is the patient with nephrotic syndrome. The kidney damage with amyloidosis is different than the kidney damage for myeloma. The kidney damage in amyloidosis is glomerular disruption and that basically creates the patient being able to shed a lot of this albumin out of the kidney in the urine. The light chain cast nephropathy that we see in myeloma is different. That affects the Cr function, while in the nephrotic syndrome, the Cr function is not always affected. There are two different ways in which the disease can present, and sometimes the urine findings can tell you at least well this is an amyloidosis or this is a myeloma in that specific scenario. The other scenario would be neuropathy could also happen in amyloidosis, but it is different than what happens in Waldenstrom's. This is an axonal neuropathy, muscle wasting, more rapidly produced, progressing. Not only a sensation issue, but pain sometimes, weakness, and sometimes hands and feet are affected at the same time, which is not precisely length dependent like Waldenstrom's is. And the other one is patients with cardiomyopathy, they have a high restrictive cardiomyopathy, cardiomegaly, macroglossia…that is the classic associated with amyloidosis. Factor X deficiency with the raccoon eyes and other bleeding problems. So any of those clinical aspects or features of the patient can make you suspect somebody has amyloidosis. And for amyloidosis, you need to get the tissue. If you suspect the patient has it and an abdominal fat pad biopsy or a transrectal biopsy can sometimes help you. The problem here is there are multiple types of amyloidosis. The one that we're talking about right now is the light chain amyloidosis, the one that is related to the plasma cell dyscrasia but you have so many other types. You have the double A amyloidosis, the TTR amyloidosis, some of them are acquired, some of them are hereditary.

So, the fact that you take a piece of tissue and look under the microscope and find the congo red, that doesn't really tell you it's a light chain amyloidosis. You still need to send that piece of tissue to the mass spectrometry. There are different institutions in the United States that can run that. And then you can actually make a diagnosis of an amyloidosis. Just to give an example, a patient present to my clinic with Waldenstrom's and cardiac amyloidosis to be treated for cardiac amyloidosis. We decided to do additional testing. We took a piece of that myocardium and the patient had actually TTR amyloidosis.

The worst thing I could have done for that gentleman is actually give him chemotherapy for this amyloidosis, because that was not going to fix it.So, always biopsy and always try to find the tissue that you're looking for before you expose the patient to treatment they might not need, and that's a good message for these types of patients.

MATT:

Stuart and Nora, I don't know about you, but I don't feel quite so bad about not understanding all this before this recording because it does get really complicated. So, I think referrals to you to sort stuff out on that end. The illness scripts that I think we can definitely remember: myeloma, we'll think about the CRAB symptoms that you mentioned; Waldenstrom's, you'll have anemia plus neuropathy and maybe hyperviscosity; and then for amyloidosis, it is more the cardiomyopathy nephropathy symptoms that we think of. I know we wanted to talk a little bit about the hyperviscosity just because I don't know if I've ever seen it, and I know if we don't ask you about it, we'll be kicking ourselves. How does that present with Waldenstrom's and how often is that? Because I don't think I've seen it or maybe I didn't recognize it.

JORGE:
So at this time I think probably about 10% of patients with Waldenstrom's can present with hyperviscosity. That range has actually decreased over time, and I think it is because we tend to detect these patients a little bit earlier. Now, the classic presentation of hyperviscosity is recurrent spontaneous nosebleeds. And they are really really hard to control, just gushing out nosebleeds out of nowhere. And the other thing is the headaches, usually early in the morning and they never go away, it gets worse over time. And the last one that's classic is blurred vision that doesn't correct with glasses. These patients tend to have these fundoscopic exams, and they have all these different changes in the retinal vessels, anywhere from engorgement and tortuosity of the vessels all the way to sausaging and all the way to actual retinal bleeds. And once you have seen a patient losing his sight or stroking out because of hyperviscosity, you never forget it and you take it very seriously. So the answer there is to plasmapherese these patients. If you suspect the patient is having these problems, either place a peripheral line or a central line to plasmapherese these patients as a right answer always. Now a teaching point here is that because the blood is very viscous and very thick, you tend to bring more fluid into the intravascular volume, and these patients can actually be artifactually more anemic than usual. You can see a Hgb of 7 in an IgM of 7000 and the patient is having all these hyperviscosity symptoms, then you might feel you want to transfuse these patients before plasmapheresis them, that is not the way you want to go. You want to plasmapherese them first and don't be surprised if the Hgb actually goes up a point or a point and a half just by plasmapheresing this patient. And then the patient might not even need to be transfused. The point is if you transfuse a patient with hyperviscosity, you actually make them more viscous, and you can actually make the symptoms worse in that specific scenario.

NORA: Is there a specific level of IgM at which you should be particularly suspicious for hyperviscosity?

JORGE:
Yeah, we actually did a study of about 800 people with Waldenstrom's and we followed their IgMs. At below 3000, almost nobody had hyperviscosity, so I would say the hyperviscosity problem starts at about 3000 mg/dL. Now the risk of hyperviscosity above 4000 was about 2-3%, between 4000 and 5000 was about 6-6%, and between 5000 and 6000 about 10-12%. Over 6000 is when it really went up to about 50-60% of the patients actually had hyperviscosity symptoms. So as you can see, it is not a linear distribution of the risk of hyperviscosity based on

the IgM. So anybody over 3000 can have hyperviscosity, but anybody over 6000 is highly more likely to have hyperviscosity.

MATT: I think we're gonna have to get take home points. We could probably go for another hour or two with all the questions we have, but can you give us, maybe if people were just going to remember 2 or 3 things from this talk, what would you like them to remember about MGUS and the 3: myeloma, amyloid, and Waldenstrom's that we talked about?

JORGE:
I think having a high degree of suspicion and just keep your eyes open for these types of things is probably the best message I can provide, just think about it. Just by thinking about it you can potentially do a workup that is potentially important. And again, an SPEP can potentially be lifesaving for people who might be having hyperviscosity, for people who might be having hypercalcemia or acute kidney injury, which is worst case scenario in here. Always have that in mind. And I think running an SPEP is a low cost, potentially high yield scenario. And then, refer to hematology.

MATT: And we now know how to interpret this too. Anything you wanted to plug before we let you go?

JORGE:
I think an important aspect of all this is we as academics and scientists and researchers, we can not advance the science without the help of our patients. And the patients can in many different ways. They can help by providing samples, by participating in clinical trials, so I encourage not only physicians taking care of patients but the patients themselves to think about participating in research so we can advance the science.

MATT:
Alright, this was awesome, thank you so much. We'll fade into the outro and let you get back to your family. I feel good about all this, and once I go back and listen like 2 times and read the show notes Nora makes and everything, I will learn this stuff so well. So thank you so much.

JORGE:
My pleasure. Thank you for the invite Nora, this was great. This was awesome. I'm glad to be able to reach out to people from different aspects of what we do and I think this is an awesome way to get the word out.