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SPEAKER 1: Greetings, I'm Dr. Gayatri Acharya, cardiology fellow at Mayo Clinic. During today's roundtable, we'll be discussing cardiac amyloidosis. I'm joined by my colleagues, Dr. Martha Grogan and Dr. Omar Abou Ezzedine, who both specialize in this area. Welcome.

**SPEAKER 2:** Thank you.

**SPEAKER 1:** Let's start by talking about cardiac amyloidosis in general. What clinical characteristics make you suspicious for this when you see a patient? Dr. Grogan?

**SPEAKER 3:** You know, many times in cardiology, we'll come to the suspicion of amyloidosis based on imaging or unexplained heart failure, unexplained atrial arrhythmias. But I would say, for many cardiologists, the first suspicion, it's going to be imaging-- either an ECHO or an MRI-- that's going to make them suspicious of amyloidosis.

**SPEAKER 1:** In addition to imaging findings, Dr. Ezzedine, what clinical characteristics-- physical exam findings-- would make you concerned?

**SPEAKER 3:** Sure. So physical exam findings are the classic heart failure exam findings. So typically-- right-sided symptoms of JVP elevation, lower extremity, edema, abdominal distension, ascites, hepatomegaly, things like this, as well as findings of pulmonary hypertension. You can have an accentuated second heart sound, for instance, and right-sided S4. But you can also, obviously, have left-sided symptoms with elevated left side feeling pressure, such as pulmonary edema, et cetera. A physical examination finding that we sometimes miss as cardiologists is macroglossia. And that's something that you need to look for to really find.

On history, typically we ask questions that are not classic cardiac clinical questions, such as a history of, for example, carpal tunnel syndrome, or spinal stenosis in more of our elderly patients, because they have also been associated with a diagnosis of cardiac amyloidosis. On imaging, typically on an ECG, you could find a low voltage. However, caution-- that's only present in around 30% of patients or so, more so in hereditary transthyretin cardiac amyloidosis, or AL.

But you can also have LVH signs on the ECG-- atrially with [INAUDIBLE] production system disease, as well. Echocardiography-- a classic is a restrictive cardiomyopathy appearing, morphology with increased wall thickness-- again, more so in TTR compared to AL, but it can occur in both. And by atrial enlargement, diastolic dysfunction and restrictive filling-- those are the main findings that the general cardiologists may come across clinically.

**SPEAKER 1:** And that raises your initial suspicion of amyloid. Dr. Grogan, how do we know, once we reach the thought of amyloid-- decide between AL and TTR? Are there differences we can tell?

**SPEAKER 3:** That's a great question because, as I've mentioned, many times cardiologists kind of come into the diagnosis because of an imaging abnormality. Although all the things that Dr. Abou Ezzedine just mentioned are really important, clinically. Having said that, so once we have the constellation of imaging findings and some clinical findings, really we cannot guess at which type of amyloid.

So if you look at ECHO, MRI, those tests, it's very dangerous to try to say, this one is AL, this one is TTR. The TTR patients tend to have even thicker hearts, and sometimes they're more well compensated. But we really have to get to the specific diagnosis.

So the key thing for cardiologist to remember is, if you're making a diagnosis of Al amyloid, you always have to have tissue. You have a tissue biopsy, either from the heart, or from another organ, or the fat. And then, we recommend typing with mass spectometry, because that is the most accurate.

So having a good pathologist-- not all pathologists are used to looking for amyloid or staining properly. So if you get a negative result, continue to pursue, send it to pathology for review. But for AL, you always have to have tissue. For TTR amyloid, as Omar is going to tell us, a PYP scan can be used if AL amyloid has been excluded with a screen test where AL are negative.

**SPEAKER 1:** And at what point do you consider the PYP scan?

**SPEAKER 2:** It depends on, obviously, the facility and your resources. But here at Mayo, we typically get that early on as a diagnostic test when you're working up a patient for amyloid. But caution-- you really have to have drawn the blood, checked for monoclonal protein, free-light chains, to make sure that you're not missing that diagnosis. And you cannot interpret the pyrophosphate scan-- which we'll talk more about-- without having ruled out monoclonal disease, because--

**SPEAKER 3:** Yeah, and just to make it clear for people-- because a lot of times when we talk about it, people say, do I really have to give this test or that test? It's not that hard. So serum free-light chains-- they're universally available, they're inexpensive. Then serum protein electrophoresis with immunofixation-- that'll be the most common way you'll hear it termed, but just make sure it's serum with immunofixation, and then urine with a immunofixation. Do those three things, learn what they are, and get them down.

We're seeing that a TTR amyloid is really not rare, especially wild-type TTR amyloid. But up to 40% of those patients will have monoclonal gammopathy, especially because it's common as people get older. So really important for a cardiologist to learn these tests. Quit bugging me about, do we need to get them? Yes, you need get them.

But then, if they're negative, you can use the PYP alone. I still often still use a PYP even early on, because if it's negative, it supports even more if everything else is pointing to AL. And occasionally, with AL patients, they can deteriorate very, very quickly. So we want to get to the diagnosis as fast as possible. So I even use a PYP in a negative sense.

**SPEAKER 1:** And Dr. Abou Ezzedine, can you explain for us what a PYP scan is and what the strengths and limitations of that test are?

**SPEAKER 2:** Sure, sure. Actually, PYP stands for pyrophosphate. And that's the tracer that we use here in North America that's FDA approved for bone scans, actually. So it's a bone tracer that has been previously described in the '80s as a potential screening tool for cardiac amyloidosis, because patients with amyloid were noted to have myocardial uptake with this bone tracer.

However, that technology back then was not pursued, because it was noted that some patients with amyloid didn't have positive scans. And we think that's probably because those were probably light-chain amyloidosis patients, rather than transthyrethin cardiac amyloid patients. And more recently, in the early 2000s, Dr. [INAUDIBLE] group out in Italy did a landmark study where they looked at patients with TTR cardiac amyloid AL in controls. And what they found was there was, indeed, myocardial uptake in TTR much more significantly, if you want, compared to ALs and controls. Now, they used a bone tracer called DPD, which is not FDA approved for use in the United States, which is why we use pyrophosphate scans here.

So some limitations of planar imaging with pyrophosphate scans is it's essentially-- a planar image is a 2D X-ray-like image of the chest cavity. And we look at myocardial uptake, either in a semi-quantitative fashion compared to bone uptake, or in a quantitative fashion as described initially by Maurer and al et, Columbia, where we look at myocardial uptake in the heart over the contralateral chest ratio of uptake. And that is thought to standardize, or normalize, for bone and soft tissue uptake. And if that H to CL ratio-- or heart to contralateral-- is over a certain threshold, then it's believed to be diagnostic for cardiac amyloidosis with a specificity that approaches 100%.

Once again, a caveat-- you have ruled out light-chain amyloidosis. And so that, essentially, gets rid of the need for a cardiac biopsy, which is quite practice changing. But it's very important that the limitations of a pyrophosphate scan be considered, and that is ruling out light-chain amyloidosis and making sure, once you're doing this scan, that you're not facing a case of a falsely elevated H to CL ratio. Such as, if there are any bone fractures in that territory, it's bone tracer. And so that can falsely elevate your H to CL ratio.

Other things in that-- anything in your chest cavity on that side, such as mitral annular calcification, aortic stenosis that's severely calcified, calcified lung nodules, et cetera. And even breast tissue can, again, falsely elevate that ratio. So you really have to be very rigorous in interpreting a pyrophosphate scan.

**SPEAKER 1:** Dr. Grogan, do we have standardized cutoffs for these ratios that we should be using? And what do you do with equivocal results?

**SPEAKER 3:** Yeah, that's a great question, because many centers use imaging at one hour. Our center and some others use three-hour imaging. So the cutoff will depend on your institution-- what you have set as your cutoff. So ours will be 1.3 for the heart to contralateral ratio. But that's very important.

People will sometimes call us up and say, oh, I have a person. They had this positive PYP scan. Here's the ratio. And when we asked the practitioner, well, when was the patient imaged? They don't know. So the protocol is really important.

And as far as when we have maybe seen false positives, we have seen one patient with plaque but no cardiotoxicity who had a positive PYP and then went on to have a biopsy. And there were a couple others that were suspicious, too. But one very definite one.

I think we have to remember that the original papers-- or all the data so far-- has been in patients who had a high pre-test likelihood of having amyloidosis-- mostly a high pre-test likelihood of TTR amyloid, but also of AL. So could there be other cardiac conditions? You know, it's possible. So with a new test, we all have to take that with a grain of salt.

Having said that, we have the consensus guidelines that we've just kind of highlighted-- that, if their screening for AL is negative, and if you have a typical ECHO and/or MRI. So that's another important thing-- not just indiscriminate screening of patients with PYP, the typical ECHO features-- thickened walls, usually abnormal strain, restricted feeling, that kind of thing, or MRI findings. So if you put those together, it is a very good test.

Some people will say, well, gosh, we're still going to have those patients with monoclonal protein, and I'm still going to have to get tissue. But that is, maybe, 40%. You still have at least 40% to 60% where you won't need a heart biopsy, whereas previously, 85% of these patients needed a heart biopsy. So it really has revolutionized our ability to make this diagnosis.

**SPEAKER 1:** And making things as non-invasive as possible, I think, is always going to be the safer option for our patients.

**SPEAKER 2:** Yeah, right.

**SPEAKER 3:** And then one crucial thing-- it is well known that AL amyloidosis can have uptake on PYP. And we've recently even seen patients with pretty strong grade 3 uptake, or more. So just make sure that you know that you need to get tissue if those AL screen tests are abnormal, because you do not want to make the mistake of thinking the patient has TTR amyloid when they have AL. The treatment will be completely different, and you don't want to delay chemotherapy because you've made that mistake.

**SPEAKER 2:** I wanted to also tag onto Dr. Grogan's response, as far as when you have equivocal planar imaging. What we have been doing here at Mayo is doing concomitant SPECT/CT imaging to specifically look at the morphology of the myocardium and where that uptake is. Is it, indeed, in the myocardium? Is it in the blood pool? And we are increasingly seeing cases that are positive on the planar imaging, on the H to CL ratio.

And then, when you actually look at the SPECT/CT, looking at the myocardium itself, the uptake is all blood pool or you're capturing, again, calcified valves or whatnot-- or a rib fracture, for example. We see those quite commonly, actually, in the nuclear lab, as well. So it's an important addition, I think, to the approach that has been initially described with planar imaging.

**SPEAKER 3:** Another thing that we sometimes forget to talk about is that PYP previously was used to grade the size of myocardial infarction.

**SPEAKER 2:** Yeah.

**SPEAKER 3:** So if a patient has had a recent myocardial infarction, then PYP is going to light up in that area. It's quite easy, even for those who do not interpret PYP scans, to learn to read them. And it's pretty simple to look at those SPECT images and see if you see it lighting up. It is it lighting up diffusely? So-- very good. Also, if you're really unsure, then get a heart biopsy.

**SPEAKER 2:** Yeah, and we typically wait around four weeks after a myocardial infarction to image the patient. It's thought the activity sort of abates after the four week cut point.

**SPEAKER 1:** So when you have an unequivocal positive PYP scan, what's the next step for our patients?

**SPEAKER 2:** So for us in the cardiac amyloid clinic, our next step is-- they have this diagnosis, again, once you've ruled out light-chain, because of prognostic and therapeutic consequences-- to proceed with genetic testing. And yes, the patient may be elderly, or what we think is elderly, but they do have children that are not. And if this is a hereditary process that we're missing, then we're not doing our due diligence as best providers. So our typical approach is, we sequence the TTR gene and look for any mutations that would explain that diagnosis.

**SPEAKER 3:** And that has come down in cost considerably. Whenever you ask about cost, you'll get different numbers. But still, it's not a very, very expensive test, as it would have been in the past. There are complementary programs through some of the various industry sponsors, too, if a person really couldn't afford the testing. But really, we just need to get it in everyone.

Even in the mid '80s, we've seen patients at 85 years old who have a pathogenic mutation. So one could argue, how much of a role did it play in that patient? But now we know they have that, and their children are at an increased risk of getting amyloid and need to at least consider genetic testing.

**SPEAKER 1:** What's required to perform a PYP scan? And what would the time commitment for a patient be? If you're referring someone and they ask you, how do you best answer that?

**SPEAKER 2:** So any nuclear lab that's performing stress testing or has access to a technician generator-- that's all you need from a radiotracer standpoint. A SPECT/CT camera is what we have here. And essentially, our protocol at Mayo-- again, a bit different than other places in that we do imaging not only a baseline or at 15 minutes-- and that's typically a five-minute scan after injecting the pyrophosphate-- but also at three hours. And that's typically a longer-- SPECT/CT scan is around 40 to 45 minutes long.

However, if you're doing just planar imaging, it's much shorter than that. So we typically have patients present, get the isotope image at 15 minutes, and then they come back at the three-hour time point for their three-hour imaging. And it's the three-hour imaging that we really use here to confirm or rule out myocardial uptake of pyrophosphate.

**SPEAKER 1:** Is it useful to receive scans from an outside institution? Are those able to be interpreted easily for continuing tertiary care?

**SPEAKER 2:** It's an excellent question. And in the ideal world, the answer is, yes. But many times, the imaging comes. We don't know what the protocol is that was used. We don't know how much radioisotope was used, what the protocol that was used at that center was.

So it may be, but there's countless times where I've needed to repeat imaging here, because of the image quality or what not. Because we don't have full access to its data that's provided, we cannot actually modify it a lot of the times-- not modify it, but sort of reinterpret it using our software, per se. But potentially, down the line, yes.

**SPEAKER 3:** And I think it's fairly easy to assess that. So we have patients now-- again, as people are starting up this imaging, people are at different points in their own laboratory of how comfortable they are, how much they've set up their protocol. But we're starting to see more where you'll get the images, you have the report, you know the sequence. And if it's all positive, you really don't necessarily need to repeat it. So I think we'll start to see a little more standardization of that.

**SPEAKER 1:** And Dr. Grogan, what's next for patients with TTR amyloidosis? What options do we have in the future?

**SPEAKER 3:** It's a really exciting time. We'll have to have another video, I think, to talk about treatment. But as many people may know, for years, wild-type TTR particularly was considered-- many would say it's an academic disease. Why are you even looking for it?

We used to call it senile systemic amyloidosis. But our youngest patient here at Mayo was 47 years old, so we got rid of that. So we know it can occur in younger patients.

So now, we have a variety of options that are just emerging both for wild-type and hereditary patients with cardiac involvement. Tafamidis is a TTR stabilizer and has been shown to reduce mortality and cardiovascular hospitalization in patients with TTR involvement, with cardiac involvement. And then, there are new drugs-- RNA interfering drugs-- that knock down TTR that have been studied primarily for neuropathy, but they'll be ongoing a new trial.

So it's really an exciting time where we've taken it out from the academic to the real world. We need to know what this is. We still don't have approved therapies specifically for cardiac involvement, but that will be coming in new clinical trials, as well.

**SPEAKER 1:** Well, Dr. Grogan, Dr. Abou Ezzedine, thank you so much for your important insights on this topic. And thank you for joining us on theheart.org Medscape Cardiology.