CME

Carpal Tunnel Syndrome and ATTR Cardiomyopathy

Discussion by Dr. Brett Sperry and Dr. Rola Khedraki

Transcript edited for clarity and brevity

Shall we ask about the history of carpal tunnel syndrome in every patient with heart failure, or do you think it should be limited to a certain age group?

Dr. Sperry**:** I do certainly ask about it, particularly in those with heart failure or heart failure with preserved ejection fraction on echo. It is to look at the images yourself. If it looks like there's increased LV wall thickness, if it looks like there's not good longitudinal movement of the heart, I will think about amyloidosis and I'll try to get patients screened and certainly ask them about these three things - carpal tunnel syndrome, spinal stenosis, and bicep tendon rupture. Our documentation specialists are really good at pulling in all outside diagnoses that a patient has.

All of these orthopedic and non-orthopedic manifestations are very common. There are several algorithms out there for early identification and they include age, sex, and race, carpal tunnel syndrome, and echo findings. Think about novel ways to include this in your medical record algorithm and pop ups.

Dr. Khedraki: For me, having a very algorithmic review of systems that go through all of the cardiac and extra cardiac manifestations is helpful. I use a phrase and it populates a list of questions and creates a framework for my note. I break it up into cardiac, musculoskeletal, neurologic, and GI systems. As I'm going through it, I'm able to visually see the number of hits that a patient has.

Shall we prospectively screen patients for amyloidosis at the time of their carpal tunnel syndrome surgery?

Dr. Sperry: This gets into how we do this. It's different depending upon what kind of institution you're in. If you're at an academic medical center where everyone is sort of under the same umbrella, it may be easier versus if you're in a private practice, which may be more difficult to get this to happen because surgeons have their own algorithms

to do things. Inserting yourself in that workflow can be difficult. I've found having a dedicated amyloid nurse navigator or coordinator is a huge help. To be able to do that on the day to day to work with the surgical teams is very important. A lot of the surgeons have PAs, nurse practitioners, and scrub teams working with them. Getting full buy in from the whole team to get this as a reminder for a surgeon in each case will get this to happen more frequently at your institution.

The surgeons love doing it, particularly when they start finding patients with minimal effort on their end. This is tissue that they're removing anyway from the area that is just being discarded. Getting this to a pathologist to look at is very simple and doesn't really add a lot to their workflow, it adds almost nothing to their operative time. Just getting it in the workflow is a little bit challenging. The other thing is figuring out who the results are going to go to. The surgeons want patients to be connected with the amyloid expert for the next steps. For us, the results go to a specific hand surgical team and then to our nurse navigator.

What organs or tissues do you most commonly biopsy during the diagnostic workup?

Dr. Sperry: The first thing to think about is if there's a suspicion for amyloidosis of the heart, how do you make the diagnosis? There is a noninvasive diagnostic algorithm for ATTR, so you don't really need a biopsy. For AL amyloidosis, you do need a biopsy. Sometimes you get it when you do bone marrow biopsy. Historically we talk about a fat pad biopsy and there are 3 types. There's a fat pad aspirate, which does take some technical expertise. There's a core needle biopsy, which our IR physicians do. It's super easy to do, but it probably has the lowest yield of all of the biopsies. Then there's an incisional biopsy where the surgeons make a one-centimeter incision and go deeper into the fat and pick out subcutaneous fat and send it to the pathologist. The highest yields here for me have been the incisional biopsy. The aspirate biopsy is probably the second. For us, the core needle biopsies have been very, very low hit rate to the point where it's not even worth doing anymore. We're doing incisional biopsies on everyone. Of course, if you still have a suspicion or the findings are unclear as far as the workup, you need to biopsy the heart which has a very high hit rate.

The second part of this is to rewind 5 or 10 years when patients have soft tissue manifestations. You're trying to pick it up early. I would personally do what I mentioned at the end of the talk, which is to think about screening patients during the surgery for the three conditions. Carpal tunnel syndrome is easy when it's open surgery. Even when it's endoscopic surgery, they can take out small pieces of tenosynovium. Maybe the hit rate will be a little bit lower because the pieces are small. Think about it in spinal stenosis and particularly in patients with a higher degree of amyloid deposition. Also think about it in bicep tendon rupture, but this is probably only going to be achievable if your surgeon does the bicep tenodesis. Surgeons can have very strong opinions on whether that's helpful to be done. Finding a surgeon that does that type of tenodesis or removal of portion of the ligament is important.

Dr. Khedraki: I've gone back retrospectively in patient's charts to see if they've ever had any biopsy, maybe from prior heart surgery, colonoscopy, or carpal tunnel surgery. I've reached out to our pathology team and asked for tissues to be stained and they're always very willing to do so. Obviously, the yield is going to be variable depending on the tissue. I think one common misconception is that providers do a bone marrow biopsy and they don't see amyloid there. Then they say, okay, there's no amyloid, but the yield of a bone marrow biopsy is only around 50%. If you don't see it and you have a clinical suspicion, you need to keep pursuing. The highest yield is always going to be the organ that's involved. If it's cardiac, you're going to have a 100% yield. In patients who have, for example, AL and nephrotic syndrome, another organ that's clearly involved would be kidney.

Dr. Sperry: Totally agree. On one side, you want to keep going and make sure you get the diagnosis. On the other side, there are mimickers for amyloidosis too. If you get the heart biopsy and everything looks negative, then you're probably done and you at least have that certainty and confirmation there.

Patients with wild type ATTR are old. Do we still need to offer genetic testing?

Dr. Khedraki: We talked about how to distinguish between AL and ATTR, but there is not any way clinically that you can distinguish between hereditary types from the wild types with ATTR. Hereditary types can present earlier on, but we're only making more diagnosis now due to increased awareness. So, we might be catching them late in the

disease process, but they could still be hereditary. I have really appreciated Martha Grogan from Mayo saying that your patient may be old, but their kids are not. So doing genetic testing has big implications on that patients' family members. I absolutely do it every single time. Taking a family history in these cases is not always going to be super fruitful because there's incomplete penetrance. It might skip generations, or it might be a later disease penetrance.

We might get negative tissue samples during the diagnostic workup. Do we need cardiac MRI in the evaluation?

Dr. Sperry: I think cardiac MRI is certainly a good test when you have a broad differential for patients, particularly with heart failure. My personal algorithm is the following. For patients who have newly diagnosed heart failure, usually done by echo finding, a lot of them will need follow up evaluation of their heart function. Usually, we do that at 3-month. I will do that with a cardiac MRI and see what we pick up there.

If patients do have ATTR, then cardiac MRI is not really the first test that you do. It's not in the non-biopsy algorithm that's been published. You really need a technetium pyrophosphate scan. Imaging modalities can be complementary, but there can be overlap with other diseases, particularly hypertensive heart disease and renal failure. So, I wouldn't hang everything on the cardiac MRI, but it can be helpful. It also provides good prognostic information with respect to ECV and T1 times. So I do try to get an MRI at some point for the amyloid patients, but when I'm initially work it up, it's usually not the first test that I reach for.

What do cardiologists need to be looking for in order to make a timely diagnosis?

Dr. Khedraki: There have been studies that have looked at how long it takes patients to get diagnosed by various specialties. It turns out that cardiology is the most likely specialty to misdiagnose amyloid. I think that part of the reason is that cardiologists can be a little bit dismissive when they see hypertrophy and they can be quick to label it as hypertensive cardiomyopathy, valvular disease, and everything else. I think that they sometimes come with their own set of biases. That's why it's so important to have an index of suspicion, be able to go through a review of systems, and have a systematic way when working these patients up.

You mentioned this earlier. Sometimes I see even cardiologists are relying too much on echo reports, rather than actually looking at the images. The majority of these amyloid patients have preserved ejection fraction and sometimes that can look like a reassuring result when you're just reading it. But it doesn't convey the whole story as far as what's going on with the patient. You look at the images and there are some really striking abnormalities, as far as small cavity size, small stroke volume, and large and dysfunctional atria. You don't get all of that from reading a report.

The other one is relying too much on the PYP reports rather than looking at the images. These are simple images to read. Sometimes these are read by radiology. But you're the one that ordered the test. You're best poised to interpret it in the clinical context. You want to make sure that spec was properly performed, that the uptake is actually in the myocardium, that you don't see any extra cardiac uptake that could be something completely different, like a rib fracture, because this is a bone scintigraphy scan.

Also, understanding that a PYP scan is an ATTR scan and that you have to evaluate AL separately with lab tests. One of the things that we've incorporated into our PYP reports is that it'll say this is a positive scan that can be consistent with ATTR, so long as AL has already been ruled out with laboratory testing. Sometimes people see a negative scan and think that the patient doesn't have amyloid when in fact they could still have AL. So, you want to be systematic and consistent with the workup and make sure that you're fully evaluating these conditions separately.

Dr. Sperry: Yeah, absolutely. I try to evaluate them separately. I try to get the PYP scan, particularly with patients who have an overlapping age and demographics. Many of these patients are in their 60s or 70s and. You could really have either type of disease in that age range. So try to look at both AL and ATTR.

You talked about how we can better diagnose this in our cardiology community. I've reclassified many people from hypertensive heart disease to amyloidosis or something else even. Maybe we can now talk a little bit about the non-cardiology side and what we can do from that side.

Dr. Sperry: It's difficult. The problem here is a lot of these signs and symptoms are very common in the general population - carpal tunnel syndrome, bicep tendon rupture, spinal stenosis, heart failure, and neuropathy.

I think all of us have seen commercials on television or on the radio for this disease. I did a couple spots on the local news for this. Then our office got barraged with phone calls saying, oh, I have carpal tunnel syndrome, do I have amyloidosis. So these are really common things. Not everyone with this has amyloidosis, 90% of people don't even have minor deposits in their synovium. But it is more common than we previously recognized, though we do have to recognize that it is still a rare disease. I think it's going to be hard for primary care doctors to really diagnose a ton of this or to diagnose a lot of any sort of rare disease. But it's important to raise awareness so that they're at least thinking about it. That's the key that you said in your presentation. So keeping it in people's minds, getting patients to the right subspecialists, and getting the right diagnostic algorithm is important. Early diagnosis is key. Early screening is key. The next phase of amyloidosis is to diagnose this earlier and get this screened earlier.

Dr. Khedraki: I agree. I wish it was called amyloidosis syndrome and treated like a syndromic disease so that people can really string together some of these symptoms that patients have as one unifying diagnosis. I think certainly if someone is above the age of 60 and has a history of A-fib, HFpEF, maybe some valvular disease like aortic stenosis, those are big triggers that should prompt someone to say, hey, maybe we should think about this or refer to a cardiology and pursue it further.

When going through the diagnostic algorithm, what do you do with mildly abnormal light chains, particularly in patients with renal failure?

Dr. Khedraki: It is a really common problem. We have to understand that light chains are renally cleared. So mild elevations are acceptable when there's renal impairment. Usually what we see is elevations in the kappa light chain and increased kappa lambda ratio. Typically, the ratio of up to 2.5 is considered acceptable as long as your immunofixation doesn't show a monoclonal protein. One thing to keep in mind, however, is that if you see a lambda predominance, so a low Kappa lambda ratio, that is never a normal finding and that really suggests a lambda light chain process. It should prompt referral to hemonc. So, again, I want to stress that AL evaluation involves looking at

kappa lambda free light chains and serum and urine electrophoresis with immunofixation. Again, the combination of all three of those tests has a greater than 99% sensitivity. At many labs including at my own institution, if you order an electrophoresis, there's an option of doing immunofixation only if SPEP or UPEP is abnormal. That's not the test that you want to be ordering. You want to be doing immunofixation regardless of what the SPEP or UPEP results are, because it's the immunofixation that's really going to be telling you what the monoclonal protein process is, whether it's an IgM kappa, for example, or an IgG lambda, or whatever it is. It's telling you that you have a gammopathy that you need to address.

What have you done within your health care system or regionally to raise awareness?

Dr. Sperry: The first thing I did when I tried to start an amyloid program was to figure out who the stakeholders are and figure out who the team members will be. From a cardiology standpoint, I had a major interest. We also had another person in our cardiology group, who had a major interest and was really involved with cardiac MRI. I'm a heart failure transplant doctor, but also an imager with nuclear, echo, and CT. So there's overlap there within cardiology. Then second, you need a hematologist who has an interest in this and have an understanding of this and a neurologist certainly for both AL and ATTR. We very quickly identified these people and assembled the team.

The second is to make things easy for people. We worked on the review of systems and getting the documentation of things like carpal tunnel syndrome into the medical record. We worked on order sets so that people would not have to remember all this stuff with the light chains, the immunofixation, and the PYP. They wouldn't have to remember what words to type in to get the right order. It was just in the amyloid order set. We also built into a little bit of education. The top part of the order set said, think about amyloid if X, Y, and Z is going on, and for AL do this and for ATR do this. Then we had all the orders below it. So we try to make it real easy for providers to order the right tests.

Then we went to our ground game, which was to shake hands and give talks to people. We did lectures. We did grand rounds to the fellows and residents in internal medicine, cardiology, neurology, and hematology. We had educational talks in our cardiology group. We gave talks to nursing and other support staff at each of our hospitals. We

kind of went around our health system. Then we worked in the community at other health systems to get some face time with some of the doctors and the teams to talk about amyloidosis and had a one-page packet to send out. We sent out a bunch of flyers about our amyloid program. I've given dinner talks in grand rounds regionally, news clips, working with nonprofits like the Amyloid Research Consortium and the Amyloidosis Foundation, getting on their websites as a referral type center, having support group meetings here in Kansas City. So that was my strategy over the course of the past few years to build something here and to get referrals and to find patients and find them earlier and earlier, which I think we've had some success.

For places that may not have adequate resources and specialized teams, what should they do?

Dr. Sperry: I think, number one, this is a rare disease and you got to get the diagnosis right and you got to get the treatment right. Oftentimes people are still learning about it, so it is best done in an Amyloid Center of Excellence, where you have more stakeholders, advanced imaging technology, and the ability to do heart biopsy. I would have a really low threshold in sending patients to your regional specialty center to because the risks are too high as far as misdiagnosing patients, getting them on the wrong treatment, or not diagnosing them, saying that they don't have it when they actually do.

When you're expanding this more and more to the community, it depends on your local expertise. If you have cardiac MRI and you have good readers, algorithms, and instrumentation, then that may be bigger in your repertoire. Or, you may have PYP. We've seen a big problem with PYP as far as getting rolled out into smaller centers and then not really having the expertise to get these read and interpreted properly, a lot of that's from the instrumentation. You can do this study on any spec camera, but you may not get good quality results if you're not using the right algorithms and if you haven't looked at a lot of these. But I think the big thing would be as we raise awareness more and more, patients will be diagnosed, more and more centers will be wanting to do this. Partnering with your centers that have the infrastructure is important.

Dr. Khedraki: I agree. I think it matters because the prognosis of these patients really depends on when the disease is diagnosed. Their prognosis worsens as they start to have more organ involvement.