TTR Cardiac Amyloid – How Common and How to Diagnose

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Dr. Friedman: Hi, my name is Paul A. Friedman, M.D. I'm chair of the Department of Cardiovascular Medicine and I have the pleasure of being joined by my colleague, Omar F. Abou Ezzeddine, M.D., C.M., M.S., who's a cardiologist, nuclear imager, head of our cardiac sarcoid clinic. And today we're going to be discussing cardiac amyloidosis, another area of his expertise. So Omar, welcome and thank you.

Dr. Abou Ezzeddine: Thanks so much, Dr. Friedman, for this invitation.

Dr. Friedman: Why don't we start with the basics. What is cardiac amyloidosis? What are the main things to know about it? How common is it?

Dr. Abou Ezzeddine: Sure. Well, cardiac amyloidosis is a pro, a infiltrative cardiomyopathy. And there's two main types of cardiac amyloid that we as clinicians should be thinking of. One is truly a medical emergency and that is light chain amyloid. And the reason that that is an emergency is, the source of the amyloid is actually the bone marrow and in the process of a monoclonal proliferative disorder, if you want. The bone marrow is secreting excessive amounts of monoclonal protein which infiltrate the myocardium and cause an acute necrotic infiltrative and restrictive cardiomyopathy. The reason that this is an emergency is, outcomes are much poorer than other types of amyloid. And these patients are typically treated with chemotherapy. And essentially, prognosis is typically poor unless we get to these patients early in their disease process to stop this infiltrative process. And that's why when we talk about amyloid, even though we may focus more on TTR amyloid in the subsequent portion of this talk, we need to keep in mind that up until the accurate diagnosis of what specific type of amyloid is made, it is considered an emergency to ensure that this isn't of the hematologic subtype. Because if it is, hematologists need to be emergency consulted and chemotherapy initiated soon as possible. The second subtype, which has garnered a lot of interest recently in the cardiology space, is transthyretin cardiac amyloid, where the source of the abnormal, if you want, protein is actually the liver. And that is transthyretin, it's a transporter protein is, either because of genetic reasons or because of age, the protein itself is misfolded and unstable. And these proteins, which are tetramers, typically, disintegrate into monomers which form the fibrils, which themselves infiltrate the myocardium, causing diastolic dysfunction, conduction system abnormalities, heart failure and ultimately death. So that second type, it's a bit more indolent. The course occurs over years. And we have the luxury of time, if you want, more so with that process compared to light chain.

Dr. Friedman: When do you suspect it? When do you think, boy, I should be thinking about amyloid here? Who should we be screening for it?

Dr. Abou Ezzeddine: Yeah. Typically, the typical suspicion arises, obviously, from a clinical presentation of either diastolic dysfunction or a restrictive cardiomyopathy, restrictive heart

failure. That is, it could be, echo findings, they could be sometimes MRI findings and sometimes based on an ECG. So it really depends on the patient's presentation. Now clinically, typically these patients present with, again, heart failure, arrhythmias, such as recurrent atrial fibrillation status post-multiple ablation attempts. They could have unexplained troponinemia (troponin leak) as to reflect the myocardial necrosis that occurs as part of that infiltration. They also could present with other associated systemic signs, particularly if it's the hematologic subtype, such as macroglossia, perioral or periorbital purpura, neuropathy, gastrointestinal symptoms, proteinuria that's unexplained. Now, if we're thinking more of TTR, there seems to be an association which is increasingly recognized with spinal stenosis and carpal tunnel syndrome. And so if you're seeing a patient who's elderly with diastolic heart failure with a history of carpal tunnel syndrome, then we should be thinking of amyloid in the diagnostic process. Typically, these patients have a preserved ejection fraction. So on echocardiogram you may see increased wall thickness, preserved ejection fraction and restrictive filling. Although as the disease process goes on over time, you could end up with some systolic dysfunction as well.

Dr. Friedman: So I'll ask you more about how we make the diagnosis in a minute, but I want to, before we were talking about special populations. There are two populations, one of which you alluded to, that are getting some attention. One is patients who have AF ablation and have recurrence. And so how often do you think we should be screening for those? The other one is patients undergoing TAVR. You know, how common is it in that cohort, how often should we be thinking about that?

Dr. Abou Ezzeddine: And to answer your question on prevalence, again, it depends on the subtype of the group we're looking at. So as you have alluded too, among patients who have undergone TAVR, studies from our colleagues at Columbia has shown that up to 16% of patients undergoing TAVR had a positive PYP scan. Up to 5% of patients with severe AS, patients undergoing carpal tunnel release interestingly, up to 10% of patients, males over the age of 50 and females over the age of 60, undergoing carpal tunnel release were found to have a diagnosis of TTR cardiac amyloid. In Spain, there's recently some data on acute decompensated HFPEF patients, up to 13% of them. Now we have done community studies here in southeast Minnesota, soon to be published, where we found that in the community population of heart failure with preserved EF, defined as an EF over 40% and wall thickness of 12 or more, around 6% of patients, 10% male, 2% female, had this diagnosis when screened clinically. Impressively, this was a sixfold recognition compared to priorly recognized diagnosis. So when we actually actively screened these populations, we increased the diagnosis by 6%. Now, ongoing studies on specific risk models to predict who we should be screening are underway and we recently, we'll be publishing very shortly, an artificial intelligence, ECG-based model, which I know you have been involved with, too, that have shown excellent discrimination and identification with an area under the curve that approached 0.9, in fact. So I think with time we're going to become better and better at recognizing what patient should be screened, based on an ECG or a specific clinical criterion.

Dr. Friedman: So between, so in other words, between 5 and 15% of people in our clinics undergoing TAVR and other settings have this important condition. We may not recognize it. The artificial intelligence ECG is one of several tools that may point us to say, hey, better think

about this. And the question is, what does it matter? Now let's focus on TTR. Why is it so important to make that diagnosis?

Dr. Abou Ezzeddine: Absolutely. For the longest time TTR and in fact, literature from the '80s would comment about how this is a diagnosis of diagnostic academic interest but without therapeutic consequences. But up until a few years ago, we now have, finally, while we previously didn't have therapeutic options, we finally have drugs, a few of them in the pipelines. One that has been FDA-approved, that has shown a 30% reduction in mortality and hospitalizations in these patients. And that is tafamidis. So not only are we, have the tools now to identify these patients noninvasively, which we can talk about here shortly, but also, we have quite effective therapies in cohorts of patients who otherwise may have not had a therapeutic option. And we're increasingly trying to move towards how do we better-phenotype specific patient cohorts such as HFPEF, heart failure with preserved ejection fraction, which as you know today, we don't have really effective therapies for. So if a certain percentage of patients in that group that is very heterogeneous have amyloid, TTR amyloid, and we have a drug that is 30% effective, you can see how the implications in our patients are quite impressive.

Dr. Friedman: How does tafamidis work and what's the patient experience with it in terms of side effects, tolerability, those kinds of things?

Dr. Abou Ezzeddine: Sure. So tafamidis is a compound that stabilizes the transthyretin tetramer. So like I said earlier, the reason that we end up with TTR amyloid pathophysiology, pathology if you want, is because this tetramer disintegrates into monomers which then form the fibrils that infiltrate the heart. So by stabilizing this tetramer, tafamidis has proven to be quite effective at not only slowing down that disease process, but also impacting hospitalizations and mortality or survival. So it's actually, this was a randomized clinical trial and the arm of patients that received the tafamidis had less side effects, if you want, than placebo. It was really, it was a very, very safe drug. No monitoring is necessary. With the clinical uptake, we've noticed some patients may have some gastrointestinal symptoms, but nothing that is intolerable, that has at least anecdotally caused me to stop the drug, ever. And again, we do not have to monitor anything for this drug. It's a very, very safe drug.

Dr. Friedman: It really underscores why the diagnosis matters. We have a drug that has almost no side effects, lowers mortality, lowers hospitalization. So it's important. And so that gets to the question, how do you make the diagnosis? You suspect it. You've got the patient. I'm thinking, hmm, is this it? What are the tests? What's your, sort of, diagnostic workflow?

Dr. Abou Ezzeddine: Sure. So as I mentioned earlier, you know, the big emergency that we never want to overlook is light chain amyloidosis, which is not hematologic process. So the first step in any diagnostic algorithm is to rule that out. And the way we do that is with monoclonal protein studies, with free light chain assessment in the plasma or CRM as well as the urine, and a mass or immunofixation to specifically rule out a monoclonal process. Now after that has been ruled out, historically, endomyocardial biopsy has been the gold standard. But as you can imagine, these patients are increasingly elderly it with multiple comorbidities. And you actually have to have access to a cath lab, which could prolong the diagnostic process, if you want. But lo and behold, we've recently in the last few years discovered that a very old bone tracer, which is a

technician-based bone radio tracer, seems to have positive predictive value after you have ruled out light chain amyloid, that approaches 100%. So essentially if you've ruled out light chain amyloidosis with monoclonal protein studies and you have a positive nuclear technician-based scintigraphy that shows that you have myocardial uptake, then, that is, really, your diagnosis is made obviously after you have suspected it with supportive echocardiographic or MRI-based imaging and this noninvasive nuclear PYP scan, for short. So it no longer is a difficult diagnosis to make. It no longer is an invasive diagnosis to make. So this has really been a huge leap, if you want, in the field of noninvasive nuclear imaging that we have stumbled upon over the course of the last few years.

Dr. Friedman: What's the role of, say, PYP versus MRI? When would you get one versus the other, if amyloid is in your mind?

Dr. Abou Ezzeddine: Sure. So MRI is a great tool and we invariably use it, even in the era of PYP. It's a supportive diagnostics tool that tells you that there's actual amyloid infiltration. But the subtype of amyloid, defining if it's light chain or TTR, it's very difficult to do that on MRI; actually it's, you can't really differentiate. So that's where, while MRI is important — it's the first step if you want — it could replace echo or echo could replace MRI sometimes, in that identifying that ok, this is an infiltrative cardiomyopathy that looks like amyloid. There are certain features on MRI which, such as abnormal myocardium nulling, elevation and the extracellular volume, things like this that will tell you, okay, yes, this looks like an amyloid cardiomyopathy. However, it does not differentiate between light chain and TTR. And for that you really need those protein studies, you really need that, what we call bone scintigraphy, because technetium pyrophosphate, it's actually a bone tracer. And we here in the States we use depletion pyrophosphate. Overseas, in Europe they use depletion DPD, which is another bone tracer that's used also for this diagnosis. So MRI is complementary but not diagnostic. And really it's the PYP scan with your light chains that are, that is diagnostic. Now there are overlapped cases. So the more we do this technique, the more we learn of caveats to its application. Because as patients get older, sometimes they have overlap clinical pictures, so that they could have a monoclonal gammopathy of uncertain significance and they could have PYP uptake. And we've found cases now where you have both processes in patients. Because the older they get, the more prone they are to something like TTR cardiac amyloid with an underlying monoclonal gammopathy, the diagnosis is really difficult and unique tissue. And so while this technique is excellent in the bulk of patients, there are certainly cases where we still depend on endomyocardial biopsy, but it no longer is the rule, rather the exception, if you want, to the diagnostic journey.

Dr. Friedman: Well, Dr. Abou Ezzeddine, thank you. This has been really informative for an important condition with the treatment really in the past few years is completely, both diagnosis and treatment, turned around and made a big impact in our patients' lives. So thank you for bringing us up to date on the topic.

Dr. Abou Ezzeddine: Absolutely. Thank you for having me and I look forward to chatting with you more about it another time.

Dr. Friedman: Thank you.

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