[MUSIC PLAYING]

TIMOTHY WONG: Thanks very much for the invitation And it's an honor to share some, I think, changes in how we provide care to our patients. And I picked the 2010 guidelines as just a marker for just sharing what's new in the field since then.

I'm involved in some clinical trials for novel drug development in HCM. And so what I'd like to focus on over the next 15 minutes is three topics. One is the increasing importance of being sure about the patient that you're treating, meaning that if you look at the definition of hypertrophic cardiomyopathy, there can be conditions that mimic it. And it's more and more important to rule those out when you have a patient with a thick heart sitting in your office.

The second topic is about an old but re-emerging therapy called alcohol septal ablation, whereby we can treat outflow tract obstruction due to left ventricular hypertrophy by causing a myocardial infarction with alcohol. And this procedure actually takes advantage of exact microbubbles that Dr. Villeneuve talked about, where we use it to guide targeting for the alcohol injection.

And then finally, I'd like to just talk very briefly about novel drug development in HCM. There are two drugs in medium and late-stage development that may change how we care for patients in the near future.

So with that, I'd like to just go over the definition of HCM and why I think it's a very difficult definition from a clinical standpoint. The essence is that when you have a patient with a thick heart, you should think about hypertrophic cardiomyopathy if there's no other good explanation for a disease that could cause a thick heart.

So it's almost a definition that relies on a diagnosis of exclusion. And because a lot of the other mimics or other phenocopies of hypertrophic cardiomyopathy are quite rare, then it's really challenging. How far do you go along and to rule out these other conditions?

And just to kind of give you an example, when you see a patient with left ventricular hypertrophy, a common systemic condition that can cause LVH include things like increased outflow hypertension, aortic stenosis. For Olympic athletes, athletic heart syndrome can mimic HCM. Cardiac amyloid, cardiac sarcoid can also mimic HCM.

And then on the other side of the spectrum, you have very rare diseases with prevalence of 1 in 10,000, 1 in 50,000 such as Pompeii disease, Fabry disease, Danon disease, PRKAG disease. And one of my fellows calls this almost like alphabet soup. They're very rare. You almost never see these in the clinical practice, yet at the same time, they're virtually indistinguishable from hypertrophic cardiomyopathy from an imaging basis.

So I thought I would share three cases about how imaging and also genetic testing can make a difference in how you care for patients and try to share with you why it's becoming more and more important.

So in this first case, this is a patient referred to the ACM center, an 80-year-old man with severe asymmetric septal hypertrophy. And you can see that the basal anterior septum is 2 centimeters, and the basal inferolateral wall is less than 1 centimeter.

There's no systolic anterior motion. So this is a patient that, for all intents and purposes, looks like it is nonobstructive ventricular cardiomyopathy. You can see that the aortic valve is calcified, but the severity of the AS is only minimal at worst.

So one very astute clinician, looking at this echocardiogram-- wasn't me-- asked the question why is the EKG tracing on this echo so difficult? And typically, when you have left ventricular hypertrophy, you get an exaggerated QRS complex. And so lo and behold, after further evaluation, a PYP study was done on this patient that showed transthyretin cardiac amyloidosis.

So this is an image taken from the American Society of Nuclear Cardiology, just to show the different grades of tracer uptake in PYP studies. And I believe Dr. [INAUDIBLE] went over this in much more detail earlier. But I think just as if you look at different cohorts of hypertrophic cardiomyopathy, every single cohort has reported a significant prevalence of amyloid in patients at an older age.

And the reason this is important is that there is now targeted therapy available. And the hope is that as more and more therapy comes online, morbidity and mortality can be reduced for this increasingly recognized condition.

So we started off with an 80-year-old man. I'm going to flip the table and look at a 20-year-old man who was referred to our center with a diagnosis of hypertrophic cardiomyopathy after a screening EKG for sports physical demonstrated LVH. He had no hypertension.

And if you look at the parasternal long-axis images on the left, it almost looks normal. The basal septum and the basal inferolateral wall look pretty normal. There is no systolic anterior motion of the mitral valve. The aortic valve is normal.

If you look at the apical forechamber on the right, then again biventricular size and function look normal. If you pay close attention to the apex, there may be some exaggerated tissue there. And a followup MRI showed apical variant hypertrophic cardiomyopathy.

You can see that on the cine on the left, the basal segments have normal thickness. As you move toward the tip or apex of the heart, the left ventricle gradually becomes thicker. And so this young man had a thickness of about 1.6 centimeters towards the apical portions of the heart. And when we gave contrast for the MRI, there was a classic fibrosis pattern near the tip of the heart where the most thickened portions of left ventricle were occurring.

So was that the end of the story? So it was for about six months until we happened to talk to the patient about genetic testing. His mom twisted his arm and said, you know, you're going to get genetic testing. And lo and behold, we were thrown for a loop.

A causative mutation in the LAMP2 gene was identified, and the reason this is important is that this actually is not hypertrophic cardiomyopathy. This is actually Danon disease, and the reason this is important is that as opposed to hypertrophic cardiomyopathy, the risk of sudden death in Danon disease is considered high enough that it warrants an automatic defibrillator.

And even more exciting is that there is now novel stem cell therapy in human trials ongoing right now that could potentially treat the actual disease phenotype, meaning that there is an enzyme that's mutated and that the stem cell therapy could actually replace it with a normal functioning protein.

The third case I'd like to share is a 45-year-old woman with no history of hypertension, with some nonspecific symptoms and underwent transthoracic echocardiography with the following images. She's about 1.5 centimeters thick, concentric LVH, and had a normal EKG. And a subsequent MRI again confirmed the echo measurements, but when we looked at the characteristics of the tissue itself, one parameter that came back abnormal was something called the T1 time.

And basically, this reflects that the fundamental composition of the muscle itself, beyond just being thick, is intrinsically abnormal. And not because of fibrosis, such as with HCM, but in this case the low T1 time was due to fat accumulation inside the muscle cell.

So this patient ended up having Fabry disease, which is a deficiency in alpha galactosidase. And it's, again, important to recognize because there is clinically available enzyme replacement therapy for these patients right now.

So I think over the course of these three cases, I wanted to show a spectrum of patients that all have thick hearts but at day's end don't have the genetic form of hypertrophic cardiomyopathy. And all three of these cases have specific treatment that is very different than what we would normally do for hypertrophic cardiomyopathy.

One question that we often get is, well, how often does it actually occur? So we're looking at several cohorts. These phenocopies are still rare. They probably occur in about 1% to 5% of hypertrophic cardiomyopathy clinic panels. So in the community, they're going to be even more rare. But at day's end, when you're treating one patient in front of you, you really don't want to miss a diagnosis that has a treatable therapy available.

So I'm going to switch gears. Hopefully, you have a better understanding of some of the thought processes behind making a diagnosis of hypertrophic cardiomyopathy. Now we turn to treatment. What we do to help our patients feel better and live longer?

So one form of hypertrophic cardiomyopathy which is the most common is what we call obstructive hypertrophic cardiomyopathy, where the thickening in the heart is located in a position that obstructs the blood that the heart is trying to pump up to the rest of the body.

So we normally treat this with beta blockers or calcium channel blockers or other medications. But when the obstruction persists despite maximal medical therapy, then we turn to talk about invasive septal therapy, septal reduction therapy. There's two forms that are in clinical use right now. The traditional form is to find an experienced cardiac surgeon to do sternotomy and then do a septomyectomy, where a scalpel is used to remove part of the thickened septum.

The other procedure is something called alcohol septal ablation. And what's changed since 2010 is that the ablation procedure that's traditionally been considered second line is being increasingly recognized as potentially a viable alternative, with some caveats.

So just to go over logistics, to keep all of us all on the same page, this is what septomyectomy looks like. The panel on the left shows a thickened basal septum with systolic anterior motion of the mitral valve.

And following surgery, you can see that the thickened septum is missing about 10 grams of tissue that has completely opened up the outflow tract. And now the heart, when it squeezes, can easily pump blood out to the aorta and the rest of the body.

So alcohol septal ablation is a minimally invasive approach, where to achieve similar reductions in the septal thickness, we inject alcohol down a septal perforator artery into the basal septum, cause a heart attack, and over time as the heart muscle thins in response to the heart attack, then the obstruction is relieved.

A lot of concerns were raised regarding this procedure in its early days. It was developed in the early 1980s. And these concerns focused on the reliance on specific coronary anatomy, the introduction of scar into the myocardium, which might increase arrhythmia risk, and other structural abnormalities.

But two registries have now demonstrated good outcomes in the medium and long term. So what does this procedure look like? And I hinted that mention of Dr. Villeneuve's microbubbles would emerge in this talk.

So if you look at the preablation coronary angiogram, you can see that there's both resting and PVC-provoked outflow gradient. You can see that there's a big difference between the LV and aortic curves on the hemodynamic data.

And then in the middle panel, the middle top panel shows a balloon that has isolated the first septal perforator artery. And we've injected a mixture of microbubble contrast and also iodinated contrast into the septal perforator, and we can actually visualize that on echocardiography.

So the bright patch in the apical four-chamber view in the still frame on the bottom shows uptake of contrast into the area that we're targeting for the ablation. And then the post-procedural hemodynamics show virtually no outflow tract gradient following infusion of alcohol.

Just to show you what this looks like without any contrast, this is that same patient, the first long-axis where you can see [INAUDIBLE] minimal outflow tract space. And a peak Valsalva gradient of 64 millimeters of mercury in a post-ablation echo, same patient showing a post-procedural gradient of 6 millimeters, which is in the top normal range.

So I think recent outcomes data have given us more confidence to do ablation. There are still risks. Probably the biggest risk we counsel patients on is at least a 10% chance of needing a pacemaker. Mortality is less than 1%. The risk of ventricle septal [INAUDIBLE] is less than 1% with modern dosing protocols. And it still requires about a five-day inpatient stay for the procedure.

So the American guidelines are being rewritten right now, and we'll see how much emphasis they place on ablation. But especially for patients who are borderline candidates for septomyectomy surgery due to frailty or other reasons, alcohol septal ablation is becoming an increasingly considered procedure.

The final thing I'm just going to briefly mention is novel drug therapy. So we talked about using beta blockers, calcium channel blockers, and on this slide, I'll also mention disopyramide as the three and only three agents that are recommended to treat outflow tract obstruction due to hypertrophic cardiomyopathy.

There's nothing else available. There's been lots of trials of clinically available therapy to see if there might be some benefit. And I think the reason I show the side is that the reason there's so many other trials is that none of them really work well.

So I'm excited to show that, though, is that there are two molecules, both of them focusing on the interest of myocardial protein myosin that bind to myosin and basically change its conformation so that it blocks the gain of function phenotype of many mutations that affect myosin and thus cause hypertrophic cardiomyopathy.

The molecule I'll talk most about is the furthest along in development. It's called mavacamten. And I'll draw your attention to the panel at the lower right of the slide. The bars depict the outflow tract gradient.

So from a clinical standpoint, if you don't remember the mechanism of action, I think the clinical take-home message is that you can often start with a gradient in the 50 to 100 range. And this can be reduced into what we would term the mild range.

Anything under a gradient of 30 is typically considered mild. So over a course of 12 weeks of therapy, you can really see that the outflow tract gradient is essentially treated down almost down to normal.

The main side effect of this medication is that there's a modest decrease in LV ejection fraction. And if you follow the solid line in that panel, the EF started off around 60%, 65%, and then at the end of the study, when the outflow gradient was minimal, it is still in the 55% to 60% range.

So this drug will probably need to be monitored. There's a phase III clinical trial underway whose results will probably be reported in the next one to two years. And if those results continue to be positive, we expect this drug to be presented to the FDA for clearance.

So in summary, I think we've kind of gone through what I think are some of the key changes or key advances in HCM therapy, meaning an increasing relevance on making sure you have the right diagnosis and avoiding specific phenocopies. Reconsidering alcohol septum ablation as another way of reducing the thickness of the heart muscle in selected patients.

And then finally, there's new hope on the horizon for targeted therapy that could treat the outflow tract almost as efficaciously as surgery but without the risk of surgery. So thank you very much for your time, and I'm happy to talk afterwards.

[APPLAUSE]