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Diagnosis & Treatment of Chronic Thromboembolic Pulmonary Hypertension

Announcer:
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Dr. Jasuja:
Okay, so we're going to transition that lovely case into a discussion of CTEPH and CTED. So to start with, we'll go through some terminology, talk about the follow-up of acute PE, CTEPH pathophysiology, and diagnosis. And then we'll talk about CTEPH and CTED treatment in terms of surgery versus BPA, and a little bit about medical therapy as well.

So in starting with our terminology, we have kind of three phrases or three categories that we'll use to describe these patients. We'll start with the post PE syndrome, which is really just defined as persistent dyspnea, exercise limitation, and impairment in quality of life that persists for longer than 3 months after effective anticoagulation therapy for an acute PE. Following, we have CTEPH, or chronic thromboembolic pulmonary hypertension, which is defined as resting precapillary pulmonary hypertension, as Dr. Channick went through, a mean PA greater than 20, with a wedge of less than 16, and a PVR of greater than 3 Woods units caused by chronic thromboemboli. Lastly, we have this group of CTED or CTEPD, which is normal resting hemodynamics but symptoms and imaging consistent with chronic thrombo pulmonary emboli.

So, we have this spectrum of disease. You can see here, all patients after PE and various numbers report symptoms of reduced functional status. After a PE, several patients have persistent thrombi on imaging, which is of varying clinical significance. Of those patients, certain patients have actual measurable limitations in their cardiopulmonary function. And then a portion of those patients are actually defined as having hemodynamically significant pulmonary hypertension with CTEPH.

So, I think the clear message to start off in evaluating CTEPH and CTED is that patients need good follow-up after acute PE. So, here's our algorithm that we use at UCLA. We have patients who are generally seen with PE in the hospital by our PE Response Team. And then if they have an abnormal echo in the hospital, we'll repeat it and see them in our clinic afterwards, 6 to 8 weeks after their acute event, at which point we'll follow up with them in terms of their symptoms, whether they have persistent RV dysfunction on their echo. And if they do have an abnormal echo, then we'll move forward to diagnostic testing, which we'll get into.

Now, the ESC and ERS guidelines have also have a very nice follow-up algorithm. And I won't go into this, it's much more detailed, but this is another resource for post PE follow up.

So now we'll get into a little bit more of what exactly is CTEPH. So we've talked about patients start off with an acute PE, several have complete resolution, up to 50% of patients don't have resolution of their clot on imaging, which again has variable clinical significance. And of those patients who have incomplete dissolution of their clot, some are not hemodynamically significant, meaning they don't have residual pulmonary hypertension, whereas some do have hemodynamically significant effects. And that's our group of patients with CTEPH.

So, there are several risk factors that we know are associated both related to the pulmonary embolism event as well as medical conditions. Obviously, having a known history of prior pulmonary embolism, although several patients, up to 25%, have never had a history of known PE and then are diagnosed with CTEPH. At the time of the PE, if you have a larger perfusion defect, is another risk factor. And then having an unprovoked PE at the time of your initial presentation.

In terms of medical conditions, we know that indwelling catheters are a risk factor, presence of a ventricular atrial shunt or infected pacemaker, having a history of splenectomy, or other conditions that lead to chronic inflammation such as inflammatory bowel disease, as is the case that Michael presented, having lupus anticoagulant positive, and having a non-O blood type.

So, briefly, we'll go into this, the incidence of CTEPH after acute PE. There have been several studies that have tried to look at this and, you know, there is a large range of published, you know, incidents from 0.5% up to 11.8%. But this was a nice study that was done that actually looked at invasive hemodynamics, and in survivors of PE, the incidence is probably around 3%. So, importantly, up to 4.8% of patients have been published who actually have CTEPH at the time of their acute PE presentation.

So I think it's important, and especially for community pulmonologists and cardiologists, to know some of the CTA findings that you can look for when patients present with an acute PE to the hospital, that may give you a clue that this is actually chronic rather than acute. So, Michael mentioned some of them on our patient's CT, including eccentric thrombus, or lining thrombus with an enlarged main PA as you can see in that second top right picture. Patients can also have bronchial artery collateral vessels which you can see coming off the aorta, and then a pattern of mosaic attenuation or mosaic profusion on the scan where the areas that are more dark gray or black are actually the normal areas and areas - or sorry, the hypoperfused areas and the areas that are lighter gray are actually the normal areas.

We also have several mimics of CTEPH that you can look for on CTA, including fibrosing mediastinitis, which Dr. Channick mentioned is now one of the Group 5 causes of pulmonary hypertension. Pulmonary vasculitis can also mimic CTEPH, we've had several interesting cases of that. Pulmonary artery sarcomas and then also lining thrombus in the PAH patient, or we also call this stasis thrombus. So here's an example of a pulmonary artery sarcoma that was resected.

So in terms of moving on to diagnosis of CTEPH. Now, the first is to suspect that it's happening, and you'll especially suspect this in patients who have a history of PE, but once that suspicion comes up, the first place to start is an echocardiogram and a VQ scan. And this can be done, you know, in the community, general pulmonologist, general cardiologist. Once those two scans come up as abnormal, that's generally the point that we would recommend referring to a specialty center that specializes in CTEPH. And at that point, we would confirm the diagnosis by performing a right heart catheterization and usually a pulmonary angiogram, although sometimes that's not needed, we can use a CT pulmonary angiogram or an MRI angiogram in the place of a pulmonary angiogram. And then, once patients are confirmed to have CTEPH, we'll then move on to assess their risk, looking at things like their hemodynamics, how high is their PVR going into a potential treatment, their comorbidities, and the specific centers' surgeon or CTEPH team experience. This is usually discussed in a multidisciplinary fashion.

So the first step we discussed was pulmonary angiography, which is actually the gold standard to confirm the diagnosis of CTEPH. It provides an anatomic map for surgery, and it involves a single injection of contrast into the pulmonary angiogram, with biplane acquisition providing the best anatomic detail. Now, it gives us information both about location and surgical accessibility. And the appearance is different than well-defined intraluminal filling defects of the acute PE, some of which you can see - we saw on the PA gram that Michael demonstrated in his case.

So here's some findings. You can see that the first image demonstrates pouches and bands. The second image demonstrates abrupt vessel narrowing, you can see in that left lung, and then we can also see abrupt cutoffs in the third photo.

So we then go on to assessment of whether a patient will go on to surgery or not. And this is, again, usually done in our multidisciplinary setting with a CT surgeon, pulmonologist, cardiologist, and interventional radiology, sometimes with the addition of hematologists as well. So there are several factors that we consider. A big portion is how hemodynamically significant is the pulmonary hypertension? So we'll look at things like how high is their mean pressure? How high is their pulmonary vascular resistance? What is their NYHA functional class? We'll also look at things like whether the patient has an advanced secondary arteriopathy which can certainly happen with CTEPH patients. And then lastly, we of course, look at the imaging that we've obtained to determine what is the best course of action for the patient. So is there proximal accessible lesions based on the CT and PA gram? Talking about patient-specific factors, patient consent, and what comorbidities each patient has. Lastly, we talk about surgical expertise, which the more experienced your surgeon is, the better the outcomes are.

So we do have certain absolute and relative contraindications to moving forward with surgery. Our absolute contraindications are, of course, if this is deemed as inoperable CTEPH, which we have other treatment options, and I'll discuss a little bit later for that group of patients, if patients have severe chronic lung disease, or if there's a lack of informed consent. Some relative contraindications include

advanced age, concomitant cardiac disease, severe RV failure, renal and hepatic insufficiency, and malignancy with reasonable survival expectation.

So talking about the surgery itself, pulmonary thromboendarterectomy, which we sometimes will call PTE or PEA, involves a median sternotomy with cardiopulmonary bypass, which enables gradual cooling to 20 degrees Celsius, and safe arrest of circulation; we call this circulatory arrest time. So once your circulatory arrest is initiated, in order to avoid blood obscuring the field, and it provides a clear operating field. It's limited to approximately 20-minute intervals, and one circulatory arrest period is enough for dissection. Then it can be completed on each side separately, so you'll have 20 minutes of circulatory arrest for one side, followed by 20 minutes of circular circulatory arrest for the other side. What is crucial to this surgery is identifying the correct plane in order to prevent perforation of the pulmonary artery, while also permitting adequate removal of the thromboembolic material. And so here you can see two picture examples of actual PTE surgery in action on the top right, and then a very nice sample that's obtained on the on the bottom right.

So we do use a surgical classification system that was created by the UC San Diego group. And you can see here that, based on the sample that is obtained after surgery, you can classify disease between level I to level IV; level I being the most proximal disease, level IV being segmental and subsegmental disease.

So we have a good amount of data and primarily from this UCSD group that has done many of these surgeries looking at, you know, improvement in PVR after surgery, improvement in cardiac output, as well as improvement of mean pulmonary artery pressure. And then you can also see on the right that there are several years of cumulative survival after PTE surgery.

Now we'll move on to discuss another treatment modality for CTEPH, which is balloon pulmonary angioplasty. And this is primarily a treatment option that we typically consider in patients who are deemed to have nonoperable disease in our multidisciplinary CTEPH conferences.

So we have several examples of data that have come out supporting the use of BPA. Here we have a 2012 article, looking at patients with CTEPH using BPA to treat. Another study from 2013, demonstrating the use of BPA in nonoperable CTEPH, and the PloS-One study from 2014, as well.

So, we have several considerations that we think about when looking at BPA as an option for nonoperable CTEPH patients. Usually, one lung is done at a time when undergoing these procedures, and 3 to 5 vessels are treated per session. Generally, patients will need 3 sets of procedures. So we have them come back and separate sessions to the hospital and we see that their hemodynamics improve over time. We generally get a perfusion scan prior to each procedure in order to be able to compare between treatments. And interestingly, lung injury is actually - the lung injury that you see associated with BPA is primarily actually for mechanical vascular injury, such as wire manipulation or balloon dilation, rather than the reperfusion pulmonary edema that you see with PTE surgery.

So you can see here that patients, before and after BPA, have favorable improvements in their hemodynamics, exercise capacity, and BPA when - and sorry, BNP when comparing before and after undergoing BPA procedures.

Now, we do have medical therapy for CTEPH as well. The guidelines do not suggest using medical therapy for patients with operable disease, it will often delay therapy. There are certain to patients in which we will consider it, but we will often use medical therapy in conjunction with BPA for patients with nonoperable CTEPH. And you can see we have four big studies that have looked at riociguat, sildenafil, Opsumit, and bosentan. And of course, riociguat is our medication that is FDA approved for use in patients with nonoperable CTEPH.

So, some treatment - a treatment - an example of a treatment algorithm that can be used for CTEPH, this is from the ESC/ERS group on their statement for CTEPH published in 2021. Once diagnosis is confirmed by an expert PH center, obviously patients will require lifelong anticoagulation, and I wish I could go into what we like to use and what was recommended for that, but that's kind of out of the scope of this talk. So then operability is assessed by a multidisciplinary CTEPH team, and if patients have technically operable disease and an acceptable risk/benefit ratio, they'll move on to pulmonary endarterectomy. However, if there's a non-acceptable risk/benefit ratio and persistent symptomatic pulmonary hypertension, or after PEA if they have persistent pulmonary hypertension, then we can move on to targeted medical therapy, which can include a combination of BPA and medical treatment.

So, in conclusion, CTEPH is difficult to diagnose, and it's important to have follow-up for patients after their acute PE events. Diagnosis of CTEPH requires a high index of suspicion, and patients should be referred to CTEPH centers early in their diagnostic workup, and PTE remains the gold standard treatment for patients with operable CTEPH, and treatment plan is formulated amongst a multidisciplinary team of physicians.

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