

**EDWARD**

All right. So what I want to do is tell you about a rare bone disease that we see in our clinic called fibrodysplasia ossificans progressiva. And what these are-- this is just an example of the types of patients that we like to see. So this is a patient, this is a nine-year-old boy. And, as you can tell, this is a photo of his back. There is this lump that is here, this is not normal. This is actually a disease process where patients get a small amount of injury and they get this inflammatory ball that just shows up at that injury site. And I'll-- I'll show you a little bit more about it later.

But this is a site of abnormal bone formation. This is the spine over here, but you can see is that this is not-- this is an ongoing process. So there's accumulation of all of these types of bone over time. It's also associated with a number of different factors, including hair loss and skin changes.

But this is the typical course-- is that you have a patient who looks pretty good at age six. Oftentimes, they are identified with this-- great toe abnormality is a shortening of the great toe. If we see this in a pediatric patient, they immediately get screened for this disease process. Because, over time, what happens is that you start seeing these different types of contractors. And what-- as you can tell from the skeleton, there's just a huge amount of extra bone that's actually present, which is better visualized here.

So this is a normal skeleton on the left hand side. This is a patient with this disease FOP. This is heterotopic ossification. This is where bone forms where it's not supposed to. You can still see the native skeleton underneath, but, basically, skeletal muscle, connective tissues, ligaments, tendons, all of those have started to convert to bone. And so these patients are incredibly debilitated. As you can imagine, it's traumatic to the families when the diagnosis is made. But as they develop and they go through their life, they-- it's a progressive loss of mobility. It's a progressive loss of function. Their cognitive function is still intact, so they need a lot of psychiatric support. But this is where-- this is an example of where case management and other types of supportive services are really, really valuable.

It's a very interesting disease, certainly, from an outside standpoint. It's clearly a very dramatic and significant phenotype. There are lots of questions. What cells give rise at this bone? This is postnatal bone formation. We typically don't think of the skeleton changing after you've been born and gone through puberty. And so this is clearly something that is going on, which-- if we could understand-- this could actually be very helpful for stimulating bone growth in adults and, certainly, for patients with bone loss. But there are very, very significant challenges.

So this is a rare condition, there's very few patients. It's 1 in 2 million, so there's 259 United States. For those of you here based in California, there's 13 based in California. Our clinic sees 39 families with this disease and they're flown here to the-- to see us.

The mutation appears to be embryonic lethal in mice, which means that we can't model this disease in mice. So we have very little in-- very, very few tools in order to really study, to understand that disease. And because of that, we actually have very few samples. Because, for these patients, it's not like-- if we draw blood, if we take a blood pressure, there are situations where that can actually trigger bone formation and we don't want to do that. So there is no-- there's very few biological samples that are available for these. We have no idea what is actually the cell type that's actually causing all of this. And we don't really know what this mutation does to different types of tissues.

So just very briefly, this is the only slide that's related to my lab work is that we have been very fortunate to take these patients, and to make induced pluripotent stem cells from these patients, take those stem cells, and use them, and combine them with patient data to really try to understand what's going on in causing this heterotopic ossification. We found that blood vessel cells seem to be a major culprit, so this is a unique, different process and that we typically think of other cell types contributing to bone. It turns out that perhaps part of the process is in the blood vessels, that there's an abnormality in the blood vessel cells that are leading to this, and that they've taken on the ability to make bone instead of maintaining their identity as a blood vessel cell.

We've also found that there's changes in inflammation, that there's different types of cell types that are associated with inflammation, this makes sense because of that-- a very traumatic link to trauma for these patients. And so we're very excited to try to tease some of this out.

But from a case management team, really, the important thing is that it has to be multidisciplinary. It really requires a modified [INAUDIBLE] palliative care approach. And we're often looking at very young patients. This is probably one of the biggest challenges is how do you help these patients through school? How do you help these patients through activities of daily living? And it ranges everything from immobility and adaptive modifications-- really trying to figure out at what point do we decide when should we be aggressive about medical treatment versus palliative care, working to keep the patients comfortable, and this is an interesting point, because when we talk with the physical therapist, sometimes we have a physical therapist who comes in really gung-ho, really wants to help this patient out, say, I am going to try to straighten their spine, we're going to try to really help them, so that they can walk again.

That's not the goal for this particular patient and I bring that up because that's, I think, an important example of the ideal multidisciplinary team is the communication to be able to say we're not looking for anatomic correction. We are looking for maintenance of functionality and trying to prevent further injuries. It's not your standard goal that some people may, may adopt as they're training-- from their training, but it's an important aspect to think about how we manage these particular patients.

And certainly social support for family, school and work accommodations, and how we maintain things like insurance coverage for these types of disease processes that can be lifelong and very significant. Oh, right, I'm sorry, the physical rehab, which I was talking about-- physical accommodation, not anatomic correction.

So, at least, for FOP we're very interested in understanding what are the causes of this bone formation, looking at inflammation, whether this bone formations can actually be harnessed for other types of disease processes, and, really, the big step now is the translation into the clinic. And one aspect is that this disease is actually probably relevant to other conditions of abnormal bone formation. So this process of heterotopic ossification can occur after blast injuries. And so for patients who have served-- so in the military and served in the Middle East-- many of them are now surviving these IED explosions, and blast injuries, and what we're seeing is that there are a number of patients who come up with this, which is heterotopic ossification in the stump. And being-- this process turns out to be very similar to what is seen in FOP.

And so trying to understand the disease-- the genetic disease-- we're hoping will actually help this with heterotopic ossification. But, again, many of the same issues in terms of patient care and patient management arise. Genetic causes, obviously, brain trauma, and hip replacement surgeries are also associated with heterotopic ossification. So trying to understand how those are linked as well as other types of diseases-- so vascular calcification and tissue calcification, which are very, very common those-- valve classifications in atherosclerosis. We're hoping that this will also give us some insights into those disease process.

And the final aspect that I want to leave you with from our clinic is actually the critical role for ancillary providers to really identify things like clinical trials. So for patients with FOP, where there is no good, effective medical treatment, having people thinking enough to say, hey, this is rare, but I've heard that there's somebody actually doing a clinical trial with an experimental treatment. Physicians sometimes do it, although that sometimes gets a little difficult attempt depending on how busy their ta-- their schedules are.

But having other members of the team being aware and thinking is-- oh, well, you know maybe we should look at clinical trials that governs and see whether or not there might be a trial that would be helpful for these patients is really valuable. And so for FOP our sites is actually very interested in clinical trials for both understanding the disease process as well as a Phase II trial supported by Clementia for testing of this medication called palovarotene. And palovarotene is related to Accutane, which was a medication used for treating acne.

It turns out that-- so Accutane is a teratogen, and fetuses who are exposed to Accutane, or retinoic acid receptor gamma agonist, develop limb malformations. And the limb malformations are because the medication blocks the cartilage and bone development. So we're trying to take advantage of that side effect for these patients to try to block the abnormal bone development that occurs. And so we've been very fortunate to be able to do that. This is an example of a mouse that has heterotopic ossification where we give-- where the-- not we-- the people over at the University of Pennsylvania provided the mouse with retinoic acid receptor gamma agonist and we're able to show that this medication is able to block this, at least, in mice. And so we're very hopeful that this will actually be helpful for the FOP patients.