[MUSIC PLAYING]

SPEAKER 1: I chose the title for the talk about polymyalgia and giant cell arteritis, and from the etymology, from the origin of those words, and what did they really mean, how did we get to those concepts, and to help you with a clinical understanding. To begin with history-- and sometimes when we're thinking about arthritis-- Sir William Osler had this famous statement about what I do every day. And he said, our father of modern medicine said, "When an arthritis patient walks in the front door, I feel like leaving by the back door." Now, Osler was the person who understood that lupus had systemic manifestations. Before him, it was thought to be a dermatologic disease.

And there is this complexity. And I would hope today that we've really helped within the course to take it when we look at a board like this and to be able to clarify. And I'm going to take an area that I remember in 1972 when I was an intern of when an article came out in the Annals of Internal Medicine about doing biopsies of the temporal artery on every patient with polymyalgia rheumatica. And there was complexity about these illnesses, of how are they related, are they related. And I'm going to, I believe, show you how to think about them.

Certainly, we see a lot of people with arthritis. And as people get older, we see many more. And so it is a great challenge. And there are certain clinical situations that we are confronted with that we have to address frequently. And these are two of them. One is an older individual who presents with bilateral shoulder pain. That's something that we see. And also, an individual who presents with temporal headaches. So do those people have PMR? And does the woman have temporal arteritis? Or do they have both? So this is our goals. We're going to review the clinical manifestations about PMR, the diagnosis, pathophysiology, and giant cell arteritis and really consider whether they are entities.

Sometimes we wait till the end of the talk to give you the conclusions, but I want to give you the conclusions and then I'm going to give you the information. And if we think about PMR and giant cell arteritis, they are related inflammatory conditions. We still don't know what causes it, and I'm going to talk to you about an enormous advance, however, about this. These occur in individuals over the age of 50. And so, are they one disease or overlapping conditions? It's important just to note a fact such as this, that 40% to 60% of giant cell arteritis patients have polymyalgia. And we certainly know that patients with polymyalgia may have developed giant cell arteritis. And these are common conditions. You know, it's estimated that up to 2% of women will have polymyalgia at some time in their life. And there are some definite target populations which you have to remember because it helps in terms of making the diagnosis.

We really do not have good treatments except for corticosteroids. There's some new therapies that have been introduced, but steroids really are the mainstay of treatment. And if we look at the published evidence about these conditions, the data is very minimal so we don't have perfect answers. But there's no question about it that these people do need to be recognized early. The earlier we do recognize them, it appears that the shorter the course may be. But a number of individuals really may need to be treated for three to five years. And we don't like to continue corticosteroids for that duration of time. But the concept of changing and decreasing the dose is something that we really must address and it has to be done gradually.

So let's take a look at this information and let me give you the whole background behind this. So polymyalgia, where does the term come from? Poly-, these are all Greek terms, many. Myo-, muscle. -Algia, pain. That's what these people have, pain in many muscles. The term rheumatica was added. The Greeks had this fascination, which was probably not a bad idea, of the various humors going through the blood. Galen introduced this whole concept of joint diseases caused by the internal flow of the watery humors.

And so when we think about it and we go back to this term polymyalgia, something that is very interesting to me that the term polymyalgia rheumatica was not introduced until 1957. There was this paper by Barber in the Annals of Rheumatic Disease. He was a practitioner and recognized that, in fact, this was not the same. Ted gave a really great talk on the spondyloarthropothies. And we used to call the spondyloarthropothies rheumatoid variants. Well they are not variations whatsoever on rheumatoid arthritis. And polymyalgia is not a part of the spectrum of rheumatoid arthritis. Remember he said to you it was the late 1880s that it was amazing gout, osteoarthritis, and rheumatoid arthritis weren't separated from each other until that time. And there were these other terms. It was fibrositis, this peri-- extra-articular rheumatism, and the one designation, this anarthritic rheumatoid disease. And that's very important to remember because these patients do not have overt synovitis that we can see like we see with rheumatoid arthritis.

So polymyalgia, pain in many muscles, is a very discrete clinical entity. These are individuals almost always over the age of 50. The onset is frequently very abrupt. Abrupt such that patients will tell you that they went to bed and they felt okay, and the next morning they woke up and they had this morning stiffness, this aching in their shoulder girdles and in their hips and proximal thighs, the hip girdle regions. And it doesn't have to be in both, but certainly this stiffness lasts for more than 30 minutes. And it certainly does persist. We see when measuring inflammation, the sedimentation rate-- again, a very nonspecific finding-- is accelerated.

So these are the features. And just to give you an idea of-- we do have this pain in the shoulder region, upper arms, the hip girdle was somewhat less involved. But I see a lot of individuals who come in, and they have bilateral shoulder pain. They have bilateral hip, lateral thigh pain especially. They may have some additional manifestations, occasionally with fever, malaise, anorexia. When we take a look at this whole situation, we see that these laboratory studies-- but again, they're very nonspecific-- they're just indicators that there's some inflammation going on.

When we take a look at the epidemiology of this problem, the average annual incidences, there are 52 cases per 100,000 people. And so this really gets to a prevalence of about a half to a little under 1%. So that's a lot of people who have this disease. And it does occur throughout the world so it's just not localized here. But some interesting aspects when we look at the pathogenesis of these problems, that in Europe the frequency decreases from north to south, not unlike sarcoidosis if you'll think about that.

And so, what is it that causes that? If we take a look at ethnic groups, we see that Caucasians are much more commonly affected than other groups. In fact, PMR is only occasionally seen in African-American individuals. Females are more commonly affected than males. And if we do look at this problem, the incidence does increase with advancing age. The median age of diagnosis is in the 70s.

So think about the differential diagnosis. Now it's not huge, but I want to consider some of them for you. And if we take a look at this whole issue, one consideration certainly is when someone comes to see you with an area of their body being affected, you have to ask yourself, is this a regional musculoskeletal disorder? And it is not common for individuals who have a regional problem to have both shoulders. It's usually just one shoulder is involved. Now there can be some variation in this. Some people can have one side more affected than the other. But just think about it. These are the common regional musculoskeletal disorders, rotator cuff tendinitis, the olecranon bursitis golfer's elbow in the sac. But remember, bilateral shoulder problems usually is not a regional problem unless there is something very specifically that the patient tells you. Activity-wise, it could have precipitated that.

When we take a look at other conditions, fibromyalgia. Fibromyalgia, these people do have pain but they have much more neck, low back-type difficulties. There is much more generalized musculoskeletal pain. If we look at polymyositis, really not a common but a significant problem, these people don't have pain, they have weakness. So if you have significant myositis, those people are not describing pain. Similar with steroids, if people had been on long term steroids-- fortunately not as much as had been in the past-- they have much more weakness than pain. If one looks at thyroid disease, hypothyroidism, it's certainly in the differential. And you should really check that over. And we heard as well about statins. The whole statin myopathy-type issue is something that should be considered as well.

A whole issue that has been considered is about polymyalgia and late-onset rheumatoid arthritis. Rheumatoid arthritis certainly can occur in the 70s, but there are really differences. And one of the differences is the amount of synovitis. Rheumatoid arthritis, as I'll show you, has inflammatory arthritis occurring in particular areas, such as the small joints of the hands, EMC/Ps and PIPs. That's really not what occurs in polymyalgia. Remember that term, the anarthritic type. And so that really is the single most important differentiating factor here is if you've got inflammation occurring in the small joints of your hands, as well as you can have the shoulder symptomatology. There is the so-called polymyalgic of rheumatoid arthritis. But certainly with people with RA, if their rheumatoid factor or their CCP-- they should be checked-- are positive, that would help. But otherwise, they're really not good ways to distinguish.

So this is just to remind us about this predilection for the small joints of the hands and feet. Remember, rheumatoid arthritis represents an intense inflammatory reaction going on within the synovium. And that certainly is a different kind of process that we see in polymyalgia. And this is what we see in these. And you know it's interesting, you cannot find a histopathology of polymyalgia.

Looking at biopsies, this is what we see here, and this is looking at the different studies. Looking here at an ultrasound, we see a fluid within the subacromial bursa. So we see a bursitis in these patients. We see here looking at an MRI that we see this as a bicipital tendinitis right in here. We can see this bursitis again occurring in this. And then looking at a PET scan, we see that there is an inflammation occurring in the shoulder girdle region.

So that's what we see. But we just do not see synovitis occurring in the small joints of the hands. It shows us the lower extremities. And what we see here, again this is the ultrasound looking at the trochanteric area-- not a test that we would do commonly-- and the same type of situation right in here looking at these areas, we see this evidence on CT scanning of bursitis. And the same findings that we saw in the shoulders, we see in the hips of this increased uptake right in here on PET scanning. So what we're seeing is an inflammatory reaction that's occurring at a different site. You know it's interesting, Ted showed you when he looked at the spondyloarthropothies, there's some synovitis that occurs here, but we also have inflammation on the tendinous attachments that are occurring in there. So the different kinds of arthritis affect different parts within the joint.

And so when we think about this and about the etiology, we just don't know what causes this. But we've heard a huge amount in the course of our different lectures about the microbiome and all these organisms in our body. And it's becoming increasingly clear that conditions like rheumatoid arthritis are very probably related to an infection somewhere, either in the mouth or upper respiratory tract and perhaps the GI tract. And we'll be talking about how this may be applicable here in understanding the relationship between PMR and giant cell arteritis because they are absolutely linked.

And so the question that comes up, as you've heard in a number of other disease, we have genetically predisposed people. And I think that a bottom line that we have to take away that there is a variation in our response to various challenges from our environment and our immune system is certainly very true within there. And so when we have a certain way that we're going to respond immunologically-- and remember the function 1 through 10 of our immune system is to fight off infections. That's it. And so that's what we're doing. And I'll show you a little bit more and then we'll talk about the cytokines.

And we have not been able to identify-- and I think when you saw looking at personalized medicine of all of this genotyping, we have 22,000 genes-- how those genes work in terms of all of these processes and how can we identify what information will help us. We certainly don't know, but I can certainly show you this is that there's certain cytokines, those proteins that are associated with the inflammatory reactions, are certainly associated with these symptoms. So then take a look at that, we see this Venn diagram and we see that if we have polymyalgia, some of those patients are going to have giant cell arteritis. Now the real question is going to be and I'll address with you is it may be that all of those patients have giant cell arteritis.

There was an autopsy study done, as we're introducing about giant cell arteritis, in 1972. It was a Scandinavian study. And there were 13 people who-- they do autopsies on everyone-- and they looked at an older population. And these were individuals who had no giant cell arteritis symptomatology whatsoever. And at the time of autopsy, in many of those individuals, most of those individuals, they found evidence of asymptomatic giant cell arteritis on some part of their large vessel vascular tree. And so we need to think about that. Are we looking at really-- not so much that there's this part of it-- but are these really entities in which there is an inflammation going on somewhere within the vasculature.

So when we take a look at PMR treatment, the disease is dramatically responsive to steroids. You can give somebody steroids with RA, they do respond but they don't respond like this. I mean, people take the first day of it and they frequently are better. What dose to use, the American College of Rheumatology, the European League Against Rheumatism have come out with criteria. And so the dose is somewhere-- I think 12.5 milligrams is low. We used to give people 35 milligrams. The dose is somewhere between 25 and 35 milligrams. And so you give it, and it's amazing. With this condition, you need to bring the disease process under control. Usually it takes somewhere between two and four weeks and then we gradually taper it. And I'll show you at the very end about some of the taperings. And this tapering is not a science. It really is an art. And we just need to go down slowly.

And so in the course of that, is a set rate helpful? Not terribly. We really base it primarily on their clinical symptomatology. There is this variability. But the earlier you treat these patients, the better they do. There's some other things we can do. We can try NSAIDs a little bit in them. Some of the patients have some steroid sparing with that. If people have the shoulder problems you can inject them as well. There have been new studies that have come out to show that there are some patients that are pretty resistant. And it's difficult to get their corticosteroids down so we use methotrexate. The problem with these studies have been they've used methotrexate only in like 10 milligrams a week which is lower doses than we typically use them. We use tocilizumab. TAMARA is a drug that has now been used. And that happens to be an IL-6 directed attack on that.

So giant cell arteritis. So how do we think about this and how is this related. When we take a look at this, the superficial temporal artery-- this is the terminal branch of the external carotid-- it comes up in here. And so why this artery? It was always perplexing to me as to how-- well it happens to be an artery. And when, in fact, there was a physician in 1890, Hutchinson, reported a case of a man who really wasn't having much other symptoms except he had pain when he put on his top hat because of pressure right there in that area. But this is a process in which we have inflammation going on within these blood vessels. And the patients present with-- these classic manifestations are the headache, the scalp tenderness, you can see this beading, thickened temporal artery, jaw claudication, visual loss that we can see and other visual symptoms including diplopia, and then we can have some systemic manifestations as well. But one thing that I thought was so important with what David Whitcomb brought up is that not everybody has all of these manifestations. And that really does create a great challenge for us in terms of our practice.

We do want to remember in terms of these vessels-- so we have the external carotid coming up here in the superficial, but remember the internal carotid right here, is that the first branch of the internal carotid is the ophthalmic. And I'm going to show you some stuff about the ophthalmic artery and that is really one of concern. We also have vessels coming here that supply the musculature around the eye so that when we think about this issue with diplopia, the whole other issue of jaw claudication. But I must say diplopia and jaw claudication are not terribly common.

So when we look at the American College of Rheumatology in 1990 came out with the criteria for giant cell arteritis. And so it's this issue of an older individual. As you'll recall, this is the same age group that we see polymyalgia. These patients may have a new headache. That is actually one of the most common reasons that bring them to our clinical attention. They have abnormalities within the temporal artery, but as I'll show you, that is not a great finding. We see an elevated sedimentation rate. That also is not a great finding. And the gold standard for this problem is a temporal artery biopsy. We need to have a relatively low threshold for obtaining a temporal artery biopsy. It's a pretty darn benign procedure. And as I'll show you, you have a hard time diagnosing this without that.

And so when we take a look at this, we can see the frequency of this about the headaches, the scalp tenderness. We have a lot of these-- jaw claudication had been reported up to the 30% or 40%, this eye symptoms, this sudden visual loss. I was just talking to one of our colleagues about a patient he had who had headaches and did develop loss. And I'll tell you once that occurs, it frequently does not come back. So that's something to be very concerned about.

And then we'll see about this stroke, and the strokes occur primarily in the vertebral artery system. And I'll show you that when we look at the involvement in some pathology study that happens to be one area that can occur. I must say although it does mention hearing loss, it's not something that I've ever seen. And this dizziness is not-- This whole issue we're going to come back to because there is just no question about it in these patients who have temporal artery involvement, there can be involvement in other vasculature areas.

Polymyalgia is a common symptom. In these patients, 20% to 65% really do have this as an additional manifestation. And one other that I want you to remember-- and I see about one case of this a year-- somebody presents with an FUO, and they really don't have anything else. They don't have headaches, they don't have polymyalgia. And if they have an FUO with an elevated sed rate, certainly that is one presentation of giant cell arteritis.

I put this kind of first. This is the day that I'm going to show you, to summarize this, but this was a study-- or a review in the annals that just took a look at these manifestations. And it turns out that jaw claudication has a very high predictive ratio with the positive biopsy. Diplopia as well, transient diplopia. And if you have this prominent, enlarged-- but look at this. The problem is headaches does not, elevated sed rate does not within there.

And so when we think about these, many of these clinical features aren't really helpful in predicting whether the patient's going to have a positive biopsy or not. And it used to perplex me greatly, but it doesn't anymore. Because if you have a relatively low threshold for doing a biopsy, if you're thinking about the problem, that really will answer it for you. Remembering that jaw claudication, diplopia are helpful, but you just can't rule it out by history. And if we look at this physical examination-- remember this-- you have synovitis in your hands and the rest, that certainly makes polymyalgia or giant cell arteritis much less likely. And this beaded, prominent, enlarged arteries-- but again, I see a lot of people in consultation and we just don't see that that often. But the problem is that they're really not perfect because a lot of people have a little bit of prominence of their temporal artery and it's difficult.

Let's put this whole sed rate to sleep about this. So, it is useful if your sed rate is low. And if it's low of less than 30 and even less than 50, the closer you get to 50 makes the likelihood ratio go up a little bit. But it's interesting that if you have a sed rate over 100, that's not that great either. It only increases the likelihood ratio to 1.9. It's helpful if it's 100, but it's far from perfect. And so it is a dilemma. And when we think about the sedimentation rate, the sedimentation rate is a poor man's protein electrophoresis. That's it. Because essentially we're looking at red blood cells that have a little negative charge. And if you have an inflammatory reaction, you make fibrinogen, and fibrinogen interacts with that so the red cells just kind of clump and so they fall more quickly. That's it. That's what an elevated sed rate primarily means, that you just have proteins interacting with the negative zeta potential on the red cells. So that's just a manifestation there. So there's nothing magical about it.

And so when we think about this is that the predictive value of a collection of features in the laboratory, it's not there. You So you're going to see people who come in with a temporal pain right in there. If they have vision symptoms, if they have jaw claudication, it certainly is of great concern. And I think this last statement of-- Because of the morbidity and this prolonged course of corticosteroids, most of us, and I as well, favor having a biopsy. If you've got a question about it, you just do a biopsy. Should you do both temporal arteries? No. You just need to, as we'll show you, you just got to have somebody who knows what they're doing and get enough of the biopsy and that's it.

But there are a couple of more pearls I want to talk to you about, what about this eye involvement and there are a couple of other things as well. This is with the study I was telling you, one of the studies, and it looked at-- this was an autopsy study-- and it looked at what involvement. This is where you have it right in here, this is the ophthalmic right in here. Here's the vertebral black as if-- at these autopsy studies, you could find evidence of the arteritis right in there. What is interesting is that the arteritis does not actually go into the skull. They call it intra volatile. It doesn't go into the-- and there's a reason apparently. And the reason that it's thought is that the internal elastic lamina-- remember you got these lamina in there-- and this internal elastic lamina, it starts to decrease as it goes into the skull. And I'll show you a picture of where the inflammation is occurring. And it happens to be starting at the internal elastic lamina.

Just a couple of things about-- remember, the ophthalmic artery is the first branch. And you get this ischemic neuropathy. And once that happens, that's a problem. You've got to treat these people aggressively and certainly remembering one thing, you can treat them right there and then. And the biopsy stays positive for-- Tony [INAUDIBLE], one of my partners was at the Mayo Clinic, and they did the studies. And it's for at least a few weeks, very probably longer. And so that this double vision is also something that does have some correlation. It just doesn't occur that often. I just don't see it. And this is what happens. You can see this optic, if you get ischemia back further or you can get-- there's a swelling of the disk or if you get a central artery occlusion.

There was this study. It's actually very interesting. So these are ophthalmologists. They looked at 363 cases who were referred to them. 106 of them had a biopsy positive. 257 were negative. And it shows you kind of what the problem is. And it shows you why you have to have a low threshold. 21% had visual loss and a positive biopsy, and they had nothing else. Zero. So that's one way it can present. So they didn't this group didn't have any headaches or anything. So again, don't be perplexed by it. It just shows you that we call it temporal arteritis. It really should be called giant cell arteritis because it depends on what area is affected.

If we take a look at these, 55% had a positive biopsy. And they did have headache, but a lot of people had headache with a negative biopsy. So that really shows you just headache isn't that great. But if somebody has got a headache, they got a new onset headache, you just got to do the biopsy. So just get it done. And this temporal artery tenderness, it helped a little bit. But a lot of people have tenderness and they get a decreased pulsation. And so it's not-- This thing worries me a little. But I've never seen a case of a normal sed rate with giant cell arteritis. I'm not sure how often that occurs.

Just a couple other points from their studies. There are these skip lesions. But got-- So if you take enough, you take an inch of the biopsy. And the pathologists have do serial sections. They're not going to see it in every section. And when we take a look at this whole situation, if you think that the patient-- especially with the headache and obviously with visual symptoms-- you should treat them right there and then. Some institutions use these ultrasounds of the temporal artery. And you can see this as a normal-- you can see this area around. We don't do that much at all here in terms of this.

I just want to, for the last couple of slides, I want to talk to you. So remember, inflammation is a very important reaction that we have in our body. And that when we look at this chronic inflammation, it just represents a reaction against antigens that we just don't process well. You look at TB and all the rest of this stuff, and we just don't get rid of that. And this chronic inflammation is huge. And we have to remember with all of these different diseases, this shows you giant cell arteritis. This is it right here. These are these giant cells right here at the internal elastic lamina. That's what it looks like. But here's something, only 50% of people in their biopsy have evidence of giant cells. And you can actually also see some periarticular, periarterial inflammation right there. And so as a consequence of this blood vessel inflammation, we really see here is that we see the ischemia with the occlusion. But also remember, especially if this occurs in other places like in the aorta, you can get dilation and you can get rupture.

So for the last minute and a half here, I want to to you about how we tie it all together. And remember we talked-- so the immune system is there to fight off infections. So what is the infections? We have these dendritic cells here with it. Remember all these cells are carried in the blood vessels, and so we do have them around. And so right here the dendritic cells involved in our innate immunity here, they gather foreign substances. And they really can result in-- here's normal with the dendritic cells. Once they get that antigen there, they really can cause a tremendous reaction. We see releasing as a consequence of various inflammatory mediators. This IL-6 is big in this. Those dendritic cells can go to regional lymph nodes. Regional lymph nodes, polymyalgia, maybe that really is how that is all explained. And then when we look at it, we see that the cytokines, they cause these reactions of fever, myalgias. The IL-6 goes to the liver, you make more fibrinogen, your sed rate goes up. And so that's really how we bring this together in a unified way.

There was a study done in neurology that came out last year that showed-- Now they did a little differently. They did 50 sections of the temporal arteries on 84 patients. And you know what they found there? They found the varicella zoster virus. DNA. And so the question is, are we really looking at a reactivation that dendritic cells pick up these viruses and that's what stimulates it. Is it only the varicella? It maybe other viruses. But this is what I think we're looking at.

And so when we look at this whole situation, the one last point that I want to make is that the problem that we have either with polymyalgia or with giant cell arteritis is what's underneath. And this slide shows that in individuals with the giant cell arteritis, positive temporal artery biopsies, in a lot of them, there can be inflammation in other blood vessels. They can present occasionally with strokes. They can present with ischemia of the bowel, ischemia in the lower extremities. I know. It worries me. We just don't see it. But you do have to worry about thoracic aneurysms such as this.

So when we look at the treatment, we treat this with higher doses, 40 to 60. And again, it's the same situation. It has to be treated slowly. I have this in here. And again, you start with those doses, and you just slowly come down. Most people, it will go away. And when we think about this, the prognosis in most of these people is good. That's why we do want to treat them early. But do remember about these vascular complications.

So here it is. We've all spent 15 1/2 hours together. Hopefully from this, you learn one little thing. And we bring together all of this information. And this PMR, giant cell arteritis, It's not that difficult actually. And I think when we look at it, we have a way to respond. We see this connection. I think these organisms are absolutely going to be critical, whether it's the varicella or not. It's going to be something like that. But I think when we come together and we think about these new concepts, it really makes it-- it makes it more enjoyable to practice. And it really means that we can give our patients the best of care.