THADDEUS OSIAL: So I don't think I've ever given a talk on the spondyloarthropathies. So it was fun to actually have to put something together-- I couldn't just borrow from an old talk. And I think it's actually a great topic. And I hope, as we go through this, you will understand why I think that.

This picture has known to generations of rheumatology fellows and probably residents and the like-- this gentleman with ankylosing spondylitis-- really, the prototype of the spondylarthropathies. And this is a corollary picture that also has been around for decades showing a man-- I believe he was in the Canadian service-- who over the years had photographs taken showing the progressive change of ankylosing spondylitis. Interesting-- the last picture, he looks better. I wonder if he may have had hip replacement-- that's the early 1970s-- so he may have had a hip replacement. Now he's standing up straighter.

But nonetheless, this is basically our concept of ankylosing spondylitis for many generations. So we're going to talk a little about the history and the specter of the diseases, the distinguishing characteristics of this family, and a little bit about pathogenesis and treatment. So he's got-- there we go. So the gentleman we just looked at-- the classic ankylosing spondylitis-- male, onset of symptoms prior to age 45, persisting disease-- months in duration, insidious onset of low back pain-- not injury, but rather progressive, persisting disease-- prolonged morning stiffness-- often awakening at night-- often a clue-- again, wakening after several hours of sleep with back symptoms-- very typically referring from the low back down into the buttock area.

I saw a man a few years ago who was in his 60s and told me that he had injured his hamstrings in playing high school football and his hamstrings had been sore for the last 45 years. In fact, he had ankylosing spondylitis, and that's why he had hamstring issues-- they weren't truly hamstring issues. Symptoms generally are not improved with the rest. There's dorsal spine pain-- another issue that is helpful-- people who hurt their back don't usually have dorsal spine pain. And that's a common finding in this family. And anterior chest wall pain-- as we'll talk, people get pain in strange areas because of the way this disease progresses. And we'll mention that a little bit later.

So that's what we usually think of as ankylosing spondylitis and the spondyloarthropathies. But here's a patient I've seen over the last couple of years who presents a different story. It's a 21-year-old woman who had several years left buttock and hip pain that was getting worse in the months prior to seeing me. She had morning stiffness, pain with ambulation, she was using a cane, some improvement with anti-inflammatories. She saw an orthopedic surgeon, who did an MRI-- she had erosions of the acetabulum, fluid in the hip-- she had inflammatory arthritis of her hip-- they were considering total hip replacement.

So I saw her and noted that she did have decreased hip motion, she did have hip disease, had some modest decrease in lumbar spine motion. But when I looked at her x-ray, not only did she have hip issues, but she had early sacroilitis. She was B27 positive. She had a set rate of 52. We began her in physical therapy, non-steroidal agents-- and eventually she was placed on an ATF inhibitor.

She's now 25 years old. She ambulates, still, with a bit of a limb related to her hip disease. She doesn't use a cane. She works as a news reporter. She recently went on an 11-mile hike in the Appalachians. And she's not had a hip replacement yet. So this is not what you usually think of as ankylosing spondylitis or spondyloarthropathy, but this is the kind of patient you can see in your office.

Very brief background-- if we go back in the 1800s, there were a variety of ill-defined arthritic conditions-- gout-- actually included more than what we recognize as gout-- acute rheumatism, chronic rheumatism, sciatica, rheumatic gout, hypertrophic arthropathies. And some diseases that we understood began to become clarified-- osteoarthritis, rheumatoid arthritis was described in the 1800s, gout became more clarified as not being a widespread illness that it was considered in past times. And as you got into the 1900s, things began to solidify a little better-- infectious arthritis, rheumatic fever, gout-- still a hodgepodge of diseases-- chronic arthritis, atrophic arthritis, hypertrophic arthritis, atrophic and hypertrophic spondylitis, psoriatic arthritis, and the like. But buried in there, you'll note, is this condition that was called atrophic spondylitis.

And so that atrophic spondylitis, in fact, was ankylosing spondylitis-- also called Marie-Strumpell's disease. Rheumatoid spondylitis-- it wasn't still clear weather it was part of RA. From a different direction, psoriatic arthritis, which again, was thought to be part of rheumatoid arthritis, but became more clear that there were differences. For example, distal interphalangeal involvement was described back in the early 1900s-- suggests that maybe it wasn't part of RA. Writer's disease, or reactive arthritis, described in the early 1900s when a gastroenterologist went through a ship-- and a certain subgroup of the sailors ended up having an acute arthritis some months later-- and enteropathic arthritis was described.

But it really wasn't until the early 1970s-- I can remember grand rounds at Presby-- hearing about HLA-B27 being associated with the condition ankylosing spondylitis. And when that happened, a few things occurred-- first of all, we understood that there was actually a wide spectrum of ankylosing spondylitis. Not just those gentlemen that I showed you on the first slide, but we found there were a lot of people that had back pain that sounded inflammatory, who didn't end up bent over like that gentlemen, yet they still had part of a spectrum of ankylosing spondylitis. And secondly, we learned that there were other diseases that seemed to be related-- besides ankylosing spondylitis. The reactive arthritis was part of this family-- uveitis was tied in-- psoriatic arthritis is tied in.

And so we went from all these individual diseases-- spondylitis, psoriatic arthritis, uveitis, reactive arthritis-- to a more unified thought of this condition of spondyloarthropathies. And that's sort of where we're evolving at this point in time. There's an inter-relationship of many of these diseases in many respects. I'll show you, clinically-- there are relationships-- and pathologically-- there are similarities between this whole family of diseases, which again, we originally thought of as individual diseases-- still individual diseases but part of a bigger family.

A quick point-- a couple of points about B27-- it's present in about 8% of the Caucasian population. But there are differences-- there's less than 1% the Japanese population, something like 10% or 20% in the indigenous populations of the northern hemisphere-- Native Americans, Eskimos, for example-- and about somewhere in the 1% to 10% range of people who have B27 positivity have an associated disease-- but it may even be as many as 20% if there's a family member who has associated disease.

Flip side-- Caucasians with AS-- 90% of them are B27 positive-- African-Americans 50%-- psoriatic arthritis-- or spondylitis and arthritis inflammatory bowel disease-- about 50%. There are more factors going on than just B27 positivity. Very quickly, the B27 is coated in a locus of the MHC. There are multiple subtypes, which is probably why-- if you have a family member with AS-- you have a greater probability-- you've probably inherited a B27 that's more associated with the spondyloarthropathies. It presents antigens to the T-cells, leading to proliferation of cytokines that are involved in the inflammatory process. But as I said, there's more to it than just the B27. We don't need to go through this in great detail, but to simply to say that-- a couple of theories-- one being that self-antigens-- as well as external antigens-- are picked up by B27 and presented to the cytotoxic T-cells, leading to cytokine production.

Another one being that the B27 has a tendency to misfolded and may have abnormal stimulation of the effector cells. So it's not clear yet what it is about the B27-- but these are some of the ideas as to why it may be associated. The key thing, though, is those effector cells then lead to production of cytokines-- has happened in so many disease-- IL-23 being a key player-- that we'll mention later-- leading to production then of IL-17, which then leads to a variety of effects. So no real sites producing various cytokines, leading to inflammation.

Other cells producing the same ones-- TNF being in there, as we will mention in a little bit. Cartilage damage and bone erosion occurring from a variety of different cytokines that are produced-- but again, these players being an important part of this process-- that then leads to new bone formation and bone damage. We don't need to remember this too much, except that here are some of the key players I mentioned-- TNF, IL-17, IL-23, TNF again-- they are key players in this process that obviously, as we get to the discussion of treatment, become important.

So first, what are some of the characteristics, clinically, of these diseases? We just talked about inflammatory back disease-- this is the slide I used earlier. Maybe focusing on a couple of things-- low back pain, buttock pain-- it's often radiation-- sometimes gets confused with-- as I said, hamstring disease or sciatica. Morning stiffness being an important part-- usually hours of morning stiffness typical-- many times awakening at night is a common manifestation-- eased by activity-- worsened by inactivity. And non-steroidals are often helpful. We often use that as an important factor. People get non-steriodals, they at least have a partial response of their symptoms.

I mentioned dorsal spine pain-- I re-emphasize that. I found it very helpful in sorting through the presenting patient. And anterior chest wall pain-- so people get sternoclavicular disease, manubriosternal disease-- I don't know that I've seen these conditions very often often in anything other than the spondyloarthropathy. I've seen swollen sternocavicular joints in these patients.

If we look at the inflammatory back problems, AS, of course, has inflammatory back symptoms-- that's the primary manifestation of AS-- so more than 80%-- some are asymptomatic or minimally symptomatic. But at least 80% have the pattern of inflammatory back disease that we talked about. Other members of this family have lower incidents, but they still have spondylitis as part of the unifying theme of these diseases. So 10% or 20% of reactive arthritis have spondylitis-- 10% of people with inflammatory bowel disease and psoriatic arthritis have inflammatory back symptoms.

To compare that, about 20% of the population has chronic low back pain-- maybe 5% of those have inflammatory back disease. Physical findings-- they're often fairly limited-- especially if you're confining it to the back-- there is some straightening of the back that may be evident on inspection-- some impaired mobility. Again, early on, these are not terribly sensitive findings-- decreased chest expansion, often occurring much later and kyphosis as time goes on. Just since people hear about Schober's testing-- it's a very simple measurement of motion as the back is flexed-- from the posterior iliac spine 10 centimeters up-- and then looking at it again. A rather crude way-- but at least it gives us something-- to be more than just its subjective appearance of loss of motion.

Decreased chest expansion-- I mentioned-- and kyphosis, which again, often occurs as time progresses-- until you finally get to this stage where this gentleman has a straight back, kyphotic appearance, actually some flexion at the hips. Now we mentioned that there's a component of this spondyloarthropathies-- it's an inflammatory back problem. But there's also a second component-- and that is peripheral arthritis. I'll make a couple of comments about the peripheral arthritis of this family of diseases. About 50% of people with ankylosing spondylitis also have peripheral joint problems-- knees, feet, for example.

It may be-- it is the predominant symptom of a disease like psoriatic arthritis. They usually present with peripheral arthritis, as does reactive arthritis, enteropathic arthritis, and what is called juvenile spondyloarthropathy. They present with peripheral joint symptoms-- and the back symptoms may occur in a subset of them. Characteristically, they're often asymmetrical and lower extremity pre-dominant. And another key factor-- they're often associated with extra articular manifestations, which we'll go into in a minute-- enthesitis, dactylitis, uveitis, mucocutaneous, and skin lesions-- and bowel lesions, which we'll get to.

So, very commonly, asymmetrical peripheral arthritis-- I see tons of patients referred by the orthopedist because someone goes to the orthopedist saying my knees have been bothering me-- I hurt it, I think-- and they drain their knee and they have inflammatory joint fluid in their knee. And they orthopedist said, this isn't a physical tear-- this is an arthritis condition. So the major differential now, in the last few years, has been Lyme disease-- where we start seeing people with an asymmetrical swollen knee. But that being excluded, this family of conditions is probably the most common reason I see it-- isolated swollen knee or a couple swollen peripheral joints.

The second manifestation is often very helpful when you're dealing with a patient with this confusing array of a couple of swollen joints and arthritis is that they often will have enthesitis, which is an inflammation at tendinous and ligaments insertion-- so Achilles tendonitis, plantar fasciitis, epicondilitis-- and they present with pain in strange places-- costal margins, iliac crest-- various sites where there is attachment of ligaments to bone-- they'll get inflammatory symptoms at those sites.

So an enthesitis, as I said, is an inflammation at a tendinous or ligament insertion into bone. There's actually research going on looking at what the heck is going on here-- what types of cells are involved this inflammatory condition here? Achilles tendonapathy-- with the swelling-- again, atraumatic swelling, or a plantar fasciitis-- these are conditions that obviously current people that don't have spondyloarthropathies. But you see them more frequently in this family of conditions. And it can often be a clue. A person with a swollen knee and had chronic plantar fasciitis. And some of the patients-- this is the worst problem they've had. We have people with a little bit of a knee swollen, but they can hardly walk because of severe persisting plantar fasciitis.

There is a condition that's called juvenile spondyloarthropathy. It used to be part of the posse articular JRA that we used to see years ago. But some of these kids present with enthesitis as a major symptom-- and they have hip disease. And it's actually called ERA-- enthesitis-related arthritis-- in the pediatric population.

Just a listing-- as I said, you can get this enthesitis clinically in lots of areas-- I don't need to read them all through-- some of which you've mentioned-- but lots of insertional sites-- and therefore, pain or discomfort in a lot of atypical sites that aren't arthritis per se. Another common manifestation-- dactylitis. So I'll see someone with a swollen knee-- and you look at their foot and they have a swollen toe, too, which they assumed they had hurt two months ago and it's still swollen. And this dactylitis is a very characteristic feature of the spondyloarthropathies due to-- it's more than just synovitis-- there's tenosynovitis that's a component of it-- so it's a longer, wider area of inflammation than you see just with a simple localized arthritis.

A second member-- so let's go to specific members of this family-- reactive arthritis used to be called Reiter's syndrome-- as many know, Dr. Reiter described in the early 1900s-- but then was found to have Nazi sympathies during World War II-- and so that name was kind of deleted-- and it's now reactive arthritis. Actually, most of the time we are not seeing classic triad-- we're seeing mainly arthritis. Sometimes these other symptoms that follow either an enteric infection or a sexually acquired infection-- it's not, per se, an infection of the joint. It's a reaction of post-infectious episode. There's some question about whether there are residual antigens from the organisms in the joints. But at least it's not an active infection that is clearly improved by treatment with antibiotics.

Here's a condition where we have an arthritis with a well-defined onset-- gastroenteritis-- some weeks later, inflammatory arthritis occurs. As I said, mucocutaneous lesions and skin lesions-- keratoderma [INAUDIBLE]. Now this begins to tie some of these things together. I've seen slides in books that will show the same picture-- one will call it keratoderma, another calls it pustular psoriasis. It is a very close similarity and it begins to tell us how these diseases do have some tie-ins together-- even clinically. And enteropathic spondylitis-- so people with Crohn's and ulcerative colitis-- 5% or 10% of them have inflammatory bowel disease that is indistinguishable from ankylosing spondylitis. They have peripheral arthritis, also. But the peripheral arthritis tends to follow the activity of the bowel disease, whereas the spondylitis tends not to.

What's very interesting is, if you take people with any of the actual spondyloarthropathies, microscopic inflammatory lesions are seen in the colon. So once again, we're starting to tie these diseases together. You can have AS-- and if you do, biopsies-- many people have inflammatory bowel lesions that are seen. It's even true in psoriatic arthritis. So if you've taken inflammatory bowel disease-- 30% have peripheral arthritis or axial arthritis-- 6% of people AS eventually develop inflammatory bowel disease. I've seen people with 20 years of AS who then develop Crohn's disease. But 60% of people with AS have subclinical bowel findings on pathological evaluation. Again, [INAUDIBLE] enteropathic ankylosing spondylitis-- some people cross over-- and then, as they said, subsets of patients have inflammatory bowel lesions.

And this wasn't planned to tie-in with the theme of the day, but interestingly, in the last year or two, there's been some studies that showed the gut-- microbiome that carries B27-- and those with [INAUDIBLE] different than non-carriers. I think we're in our infancy as far as understanding where the microbiome fits in with this family of conditions versus the colon that we just heard about. But at least there is some evidence that there's something going on there that might be part of the theme of tying these different diseases together.

Psoriatic arthritis-- again, another member of this family. I showed you this one before-- asymmetrical swollen knee. Also, asymmetrical arthritis in the upper extremities-- I'm not sure why this is so blurry, but I think the next one-- actually, it's too blurry, too, for some reason. So patients can get distal involvement. It's often asymmetrical, so it doesn't quite look like RA. You know, you'll get a finger here-- a finger there-- and actually this kind of destructive absorption is present in severe patients with psoriatic arthritis. Here we go-- nail involvement and adjacent DIP involvement being characteristic-- skip that.

Uveitis is a common member of this family-- 30% or 40% of people with AS-- and other patients with other spondyloarthropathies gets uveitis. It is associated with B27 by itself-- you don't have to have the other conditions evident clinically. And, of course, there are multiple other diseases that can present with uveitis, but the spondyloarthropathies are a common, rheumalogic cause of that.

How do we make the diagnosis? Unlike many of our rheumalogic diseases, there's not a whole lot in the way of laboratory studies. This is a condition where the history and physical-- really, the history early on-- is key. Symptoms of inflammatory back problems-- or an asymmetrical peripheral arthritis-- enthesopathy related symptoms, uveitis, some response to non-steroidals. Family history-- we'll often see a person with a swollen knee, who have no other explanation, but two siblings have psoriasis. And you begin to think that that's likely the underlying cause of their disease.

The laboratory studies-- again, unlike our lupus and other patients-- not much. Inflammatory markers in some 50%. Inflammatory joint fluid is probably one of the more important things. We'll get people with psoriasis all the time-- they'll have joint pain, which of course they do, like the rest of the population. And the question becomes-- is this psoriatic arthritis? Or is this just simply osteoarthritis? In a patient with psoriasis, inflammatory joint fluid-- besides the pattern of the symptoms-- can be very helpful in sorting through that. And the B27 is helpful, in a way, if the story fits. But again, remember 80% or so of people with B27 don't have the disease.

Imaging studies are interesting if you're looking at the back. If they have sacroiliitis the diagnosis is made-- they have ankylosing spondylitis. If the x-rays are negative, MRIs may show abnormalities early on-- this being called non-radiographic spondylitis. Because classic spondylitis-- you have to have x-ray changes. That's where the definition is now. If the MRI is negative, then you begin to wonder-- do they have inflammatory back problems? Or is it just not showing up yet on MRI?

And I've just got to show, quickly, somebody with early sacroiliitis-- they get narrowing-- actually, pseudo-widening early gets some sclerosis around the margins. On MRI, they may have edema and erosive changes-- and eventually, you can't find the SI joints because of fusion. Because of inflammatory changes along the margins, they also get this type of [INAUDIBLE] formation, where there is a bridging of one with the other along the vertebral region.

Why do we want to treat this disease? Number one-- we want to treat it because people hurt and they have symptoms. In the case of the peripheral arthritis, we want to prevent progression. Some of these conditions-- we have to understand-- don't always progress. Enterohepatic peripheral arthritis-- in my experience-- really has a fairly benign course most of the time. They'll get flares and remissions-- can be symptomatic-- but usually not terribly destructive. Reactive arthritis, we usually thought of, as a self-limited disease-- but we've all seen a few patients who've had progressive persisting destructive disease.

And then with psoriatic arthritis, we see wide variability. I see people who have episodic monoarthritis-- a swollen knee every three years-- and that's all they have-- to people that have severe deformities. So we have to pick through here-- but there are reasons to treat some of these patients because-- hoping to prevent the damage that occurs.

The spondylitis-- the back involvement-- is a little less clear cut-- certainly treatment helps symptoms-- but the question is, does it really change the course of the disease? And there's a really ongoing debate at this time-- as to how much treatment affects the course of spondylitis. It may be in the past, we haven't treated people early enough-- we maybe haven't used the right combination. Some studies have said TNF numbers plus anti-inflammatories might prevent progression, but it's a slowly progressive disease-- it's not like RA where the joints melt away in a couple of months.

Here-- you're looking at progression over years-- and it's hard to document whether we're affecting it. But this is what we're trying to prevent in the peripheral arthritis. I'm just going to skip over those couple things.

So treatment-- anti-inflammatories remain a treatment of choice. There was a literature some years ago that non-steroidals were disease modifying. If you took them continually, it's not as clear cut.

Physical therapy-- so this has been the standard treatment for years. The non-biologic agents, like sulfasalazine and methatrexate are helpful for the peripheral arthritis. It's not as clear that they do anything for spondylitis. The biologic agents have clearly been effective-- and certainly the symptoms of the spondyloarthropathies-- and these agents often will treat the other manifestations-- uveitis, enthesitis, Achilles tendon, and plantar fasciitis can often be remarkably responsive to TNF inhibitors when they've not responded to other treatment.

There can be co-benefits-- treatment may help the inflammatory bowel disease. It may benefit-- treating the enteropathic lesions-- we don't know if treatment with antibiotics helps the enteropathic arthritis problems. Psoriasis-- treating psoriasis does not help the arthritis. So there's not a clear-- that used to be thought-- but there's not a clear relationship.

The treatments include the TNF inhibitors I showed you on that chart. The TNF inhibitors are an important part of the process in treating-- of the inflammatory cascade-- and the TNF inhibitors are effective and have really changed treatment in people with severe AS and the peripheral spondyloarthropathies. Proof signs and symptoms-- synovitis, enthesitis function. They do improve MRI findings in spondylitis. But as I said a minute ago, what is not clear is whether they really change the course of the disease.

And then finally, relating again back to that cascade I showed you there-- a couple of new drugs that are out-- secukinumab, which is an anti-IL-17 inhibitor has been approved for spondylitis and psoriatic arthritis. It is a relatively new drug, so I don't have a lot of experience, but I've seen some pretty remarkable responses in patients with psoriatic arthritis, particularly. And ustekinumab has been used for psoriatic arthritis alone.

So we're seeing an evolution to some more treatments beyond the TNF inhibitors, which have been one of our standards in treatment over the last 10 to 15 years in this family. Obviously there are risks-- and many of you are aware-- infections, re-activation tuberculosis, worsening advanced heart failure risks, and uncertainties concerning risks of colon and recurring cancers.

So I think that the guy I showed you at the beginning-- the man with bad AS-- that's not a usual patient in your office. But some of these other conditions that we've talked about-- the patient presenting with unusual inflammatory conditions-- swollen joint here-- a little this-- a little that-- the spondyloarthropathies are often where one goes looking for an answer. And unlike many of our diseases, I said it's really doing a good history and physical-- and sorting through the story-- you can often come up with a clear answer as to what we're dealing with in that family. So we have treatments-- it's an important diagnosis to make.