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Putting the Puzzle Together in Axial Disease: Assessment and Management of Axial Features in Patients With axSpA and axPsA

Chapter 1: The Pathophysiology of Axial Spondyloarthritis

Announcer:
Welcome to ReachMD. This Medical Industry Feature titled, Putting the Puzzle Together in Axial Disease: Assessment and Management of Axial Features in Patients with axSpA and axPsA, is sponsored by Novartis Medical Affairs.

Dr. Christopher Ritchlin:
Good evening and welcome to tonight's program where we have two presentations. The first presentation will be SpA discussion, Putting the Puzzle Together in Axial Disease: Assessment and Management of Axial Features in Patients with Axial SpA and Axial PsA.

I am Christopher Ritchlin from the University of Rochester Medical Center. And this evening I'll be joined by Atul Deodhar from the Oregon Health Science University, School of Medicine, Portland, Oregon; Philip Mease from the Providence-St. Joseph Health Systems and University of Washington School of Medicine in Seattle, Washington, and Alexis Ogdie-Beattyfrom the Hospital of the University of Pennsylvania in Philadelphia. Now I should say that we're actually all in different locations and putting this program together, but through the magic of technology, we're all going to be on one stage, which is really quite exciting.

Here are disclosures. This presentation is sponsored by Novartis Medical Affairs and all speakers have been compensated for their time.

And the individual disclosures are under the speakers names.

The spondyloarthritis spectrum is composed of both axial and peripheral subtypes as shown on this slide. So on the left, we see those disorders that are predominantly associated with axial disease and they include non-radiographic axSpA and ankylosing spondylitis. On the right, we see those disorders that are associated with peripheral disease, and this includes psoriatic arthritis, reactive arthritis, inflammatory bowel disease-associated arthritis and undifferentiated peripheral SpA.

This shows the overview of the spondyloarthritis spectrum of disease with multiply diverse clinical features that include enthesitis, peripheral arthritis, dactylitis, axial involvement, and psoriasis, as well as other features such as acute anterior uveitis, inflammatory bowel disease, good response to nonsteroidal anti-inflammatory medications, a positive family history, and many patients are positive for the class one allele HLA-B27.

So I'd now like to discuss the pathophysiology of axial involvement. In spondyloarthritis, biomechanical stress and inflammatory factors, including infectious antigens, amplified by a major histocompatibility complex (MHC) susceptibility genes, human leukocyte antigen (HLA)-B27 variants and endoplastic reticulum amino peptidase (ERAP1), single nucleotide polymorphism transcription factors, induce specific cell types to produce a series of inflammatory cytokines, including interleukin-23, interleukin-17, TNF, IL-1 and IL-6. Hematopoietic stem cells elaborate RANK ligand, and NF-kappa B as well as MCSF, to differentiate monocytes to osteoclasts, which extend inflammatory damage in the sacroiliac and peripheral joints. Mesenchymal stem cells facilitated by Wnt and bone morphogenetic protein, or BMP, differentiate to osteoblasts to form new bone and ankylosis.

Here in this slide, we illustrate IL-23 dependent and independent production of IL-17A. Despite interleukin-23, being a key driver in the induction of IL-17, producing Th17 cells, inhibition of IL-23 has failed to show efficacy and axial spondyloarthritis or axSpA. IL-17 can be produced by several different sources in spinal entheses. Emerging evidence supports the cellular basis for IL-17 production that is independent IL-23. IL-23 receptor positive and negative subpopulation of gamma Delta T-cells have been identified in human spinus processes entheses. Figure A shows Masson's trichome stain section showing the area of the spine harvested for analysis of patients

with spondyloarthritis or SpA.

Outer edges of the spinus process are labeled peri-entheseal bone, or PEB, and they're inter spinus ligament labeled entheseal soft tissue, or EST. Figure B shows positive standing of gamma Delta T-cells that were observed in entheseal tissue at the bone soft tissue border. Figure C shows positive standing of gamma Delta T cells as in the PEB anchoring region of hematopoietic bone marrow.

This is a cartoon that illustrates both the IL-23 dependent and independent production of IL- 17A. One can see here that the blue is IL-23 dependent and the black is IL-23 independent. And so you can see that the Th17 cells and Tc17 or CD8-17 cells can really act by through initiation and persistence differently in terms of being IL-23 independent or IL-23 dependent in blue. We see that there are other innate cells ILC3, or innate lymphocytes cells type three innate NKT cells, gamma Delta T-cells, and MAIT cells, which can act via the IL-23 independent, although gamma Delta T-cells can also act through an IL-23 dependent pathway. So it's important to understand that there are different ways for cells to produce IL-17 that can be both IL-23 dependent or IL-23 independent.

Chapter 2: Case Review 1 – Delayed Diagnosis in AxSpA

Dr. Christopher Ritchlin:
Now that we've heard a summary of the pathophysiology of axial spondyloarthritis, I'd like to move to the discussion. And I want to start with a question to Atul. Can you share a case of a patient with axial SpA who experienced a delay in diagnosis and what clinical features did they present with?

Dr. Atul Deodhar:
Yeah. Thank you very much, Chris. I'm going to present a case of a 44-year-old gentleman and he was referred to the rheumatology clinic because he had chronic buttock pain, left buttock pain and arthritis, quote unquote, and the internal medicine physician who was looking after him found that he was HLA-B27 positive.

Now this gentleman is very healthy and very active. I mean, I would say actually he's very athletic. He completed an Ironman Canada race in July of 2013. And Post-Ironman race, he started getting this pain in his left buttock, and next 18 months, he went through this period when his quality of life had dramatically deteriorated because of this pain, because his life revolved around running and jogging and biking and hiking and swimming, et cetera, et cetera. And this pain would really, really bother him. He first went to his primary care doctor who referred him to physical therapy and that didn't work. So, he went himself to the chiropractor, then he went to osteopath and that did not work. He went to orthopedic surgeon that didn't work; went to a family practice sports medicine clinic, which actually injected his buttock region with steroids first and then with prolotherapy, his own blood, nothing worked. Went back to his primary care doctor after all, this 18 months of going from pillar to post, he tried rest, he tried different therapies, as I said, physical therapy, et cetera. Nonsteroidals alleviated pain to a certain extent, not dramatically. And at that last visit, after 18 months back to his primary care, they did his investigation and they found that he was HLA-B27 positive. So he was referred to rheumatology.

And I have taken this directly from my rheumatology fellows note. And this is the importance of how. We rheumatologists should really approach a patient like this. I'm very proud of this fellow. She asked him, okay, I understand your problem started after the Ironman race, but tell me what happened before that. And the patient said that, “you know, it's interesting, you asked me because I always had this low back pain. I always had this left buttock pain back to my mid-twenties.” And then the patient gave very classical history of inflammatory back pain only because the rheumatology fellow was the first doctor to ask him these questions. The pain awakened him at night, worsen with the rest, improve with activity.

At that stage in his twenties and thirties, he could take ibuprofen/naproxen, full dose that would relieve the pain completely. His stiffness was only 30 minutes, not 60 minutes is what we would think with inflammatory back pain. And he also had chronic bilateral Achilles tendon pain. He couldn't remember if they were swollen or not.

He chocked all of that to his active lifestyle. No uveitis, no psoriasis, no inflammatory bowel disease. No nothing. Now this is mid-twenties. Now this guy is 44 years old. You can find out 20 years or more have passed through that. And everybody is fixated on this Post-Ironman injury to his buttock tendon. When the fellow examined him, then she found that he had bilateral Achilles tendon insertion tenderness, tender on sacroiliac joint which is not that specific, tender on the ischial tuberosity and the piriformis area.

And we looked at his pelvic MRI, which was done by the family practice doctors way back, which actually had shown minimal tendinopathy of the origin of the left conjoint hamstring tendon, no tear.

That was his diagnosis. Which is the reason why he was getting these buttock injections of steroids and prolotherapy, et cetera, x-ray of sacroiliac region was normal. We simply asked them to send us those images, pushed to our radiology. And we found out that his left sacroiliac joint showed classical changes of bone marrow edema, fatty changes, and, in fact, erosions. His buttock pain, maybe it was also coming from his hamstring tendon, but most of it was coming from his left sacroiliac joint. This is a delay of 20 plus years in a man

who actually never really said that “my main problem is backache” because for him it wasn't. He is so athletic. He doesn't want to complain that he goes from pillar to post because of his pain in the buttock.

So, this gentleman definitely had significant amount of damage to his sacroiliac joint as shown by the erosions. So, he actually had non-radiographic axial SpA. Chris?

Dr. Christopher Ritchlin:
A question I wanted to ask you Atul was I see this delay in diagnosis being very common in very athletic young people because they deal with the pain by being engaged in sports like your patient.

Do you find this to be a rather common event?

Dr. Atul Deodhar:
Yeah, we have somehow in rheumatology said that these patients presented with low back pain. This patient did have low back pain, but his presentation was not that unless you ask him that. His presentation was buttock pain and they call it hip pain. And of course he had other peripheral spondyloarthritis, typical enthesitis in his Achilles tendon, et cetera, et cetera. And this is very important because he went over 20 years without complaining about this. And then he only complained after it became so bad that he couldn't really do his day-to-day activities. And the nonsteroidals, which used to work completely, stopped working completely after 20 years of giving him some relief.

And I would say that the main reason why, I mean, there are multiple reasons why there is a delay in diagnosis. There are, in my mind, there are three major reasons of delay in diagnosis. Number one is that chronic back pain is very common. We looked at the enhanced data and about nearly 20%, one fifth of the us population, has chronic back pain at any given time. 19.4% to be exact. That's number one. Number two, we don't have a good way of diagnosing this. There is no good biomarker to diagnose axial spondyloarthritis. And number three is that outside of rheumatology, the other physicians who take care of back pain, they are not as much in tune with the advances that have happened in axial spondyloarthritis.

So back in 2016, we did a literature review and found that 60% of the patients for their backache would see the general practitioners, primary care doctors, about one third would see orthopedist, and another one third will see chiropractor's before, if at all, they come to rheumatology. There is another study we did around the same time, which actually we looked at the insurance claims database and found that the median time from symptom to rheumatology referral was nearly a year, which I, we taught that is impossible. I mean, that overtly optimistic because then another study we were involved in called PROSpA, and that was a study of patients being referred to rheumatologists for backache, for suspicion of axial SpA, and that was more representative where we found that in the United States, the delay in diagnosis could be as long as 14 years. These people have suffered with their backache from start of their symptom, to their getting diagnosis nearly 14 years. It is unbelievable how long this prolongation is.

Chapter 3: Why Is Delayed Diagnosis an Ongoing Concern?

Dr. Christopher Ritchlin:
Atul, thanks so much for giving us a detailed explanation of why diagnosis is often delayed. I guess the other question related to that is why is delayed diagnosis ongoing concern for patients with axial SpA?

Dr. Atul Deodhar:
Yeah. I mean, so people suffer unnecessarily for long periods of time because this is the condition, for there are excellent therapies available to treat. And these people go from pillar to post undergoing various therapies for mechanical back pain, which does not really touch their immune-mediated inflammatory problem that they are happening in their back. And then there are certain countries, which actually have tried to tackle this and I can give a couple of examples, one is Germany, one is Great Britain. There, in Germany especially, they have kind of taught when to refer patients to rheumatology.

So the referral strategy has been very well denoted in Germany and also in Great Britain. And what they have found out is once they taught the other physicians, namely orthopedic surgeons, physiatrists, even physical therapists, primary care physicians, when to refer the patient to rheumatologist, the delay in diagnosis became less.

It used to be seven years or something. And then it now gone down to about three years, two to three years in Germany and similar drop in Great Britain. Now we don't have such a referral strategy in the US SPARTAN, which is of the Spondyloarthritis Research and Treatment Network, is about to take on such a referral strategy.

And I think that is what is going to help the other providers who see patients with back pain, who refer patients to rheumatology, appropriate patients to rheumatology, with some telltale signs. And that is going to reduce this delay in diagnosis. Chris?

Dr. Philip Mease:
And Chris, this is Philip. If I could just add one other point. Notice the age of this particular patient he was experiencing this in his twenties and thirties and early forties in the prime of his life, of his work life. And we know from multiple studies that there are problems with productivity in the workplace, enjoyment of activities at home. And so in addition to treating, the fact that we're not treating his symptoms, it has a profound effect on the society at large because of decline in work productivity because of the manifestations of the disease.

Chapter 4: Factors Contributing to Delayed Diagnosis and Mitigation Strategies

Dr. Christopher Ritchlin:
Thank you, Atul and Philip. I would like to ask the panel what programs in other countries have been successful in accelerating referrals to a rheumatologist? What strategies have and have not worked? And what are some common elements contributing to misdiagnosis and delay in diagnosis by rheumatologists?

Dr. Atul Deodhar:
So, as I said, the commonest misdiagnosis is mechanical backache. I mean, mechanical backache is very common. So our axial spondyloarthritis patients get diluted in the mechanical back pain, a number of patients that there are. And the second thing, of course, as I said earlier, we don't have, or the primary care doctors don't have, or nobody has a very good biomarker to suspect.

I mean, HLA-B27 could be one of them, but HLA-B27 is found in 7.5% of white Caucasian population. So, if you take a hundred people with HLA-B27, only five of them will have this condition. So, we don't have very good biomarkers and the education of these non-rheumatology providers that we need to educate them more, since we have very good treatments and the strategies which have worked are the referral strategies. Referral strategies, then tell the primary care provider that if there is inflammatory back pain type of symptoms, number one, if they have got backache and psoriasis, if they've got backache and uveitis, if they're got backache and IBD, if they have got this unexplained, perpetual sports medicine type of injury, which really is enthesitis, for no reason and nothing is working, think that there may be something wrong; this might be immune-mediated. And those types of strategies have worked in Germany and in Britain. And we need to have such a strategy in the United States.

Dr. Alexis Ogdie-Beatty:
Atul, if I can also add to that, too. I think one of the other things that we need to think about is getting this as a part of training for orthopedics, as a part of training for physiatrists and for chiropractors. So that they're thinking about this early in their training and it's not something they're trying to learn after they're already in practice. I think we have more impact of the training phase.

Dr. Atul Deodhar:
And thank you, Alexis for that. And in fact, that's precisely what Germany did. The German rheumatologists, at least in Berlin, they in fact did lots of meetings, lots of educational programs in Berlin that I'm aware of.

And that's where, because of their education of all these other providers, their delay in diagnosis has been nearly half. From seven years it has come down to three years, three and a half years, or even less in certain situations. Similar study has been shown in Britain also that the delay in diagnosis has been reduced just by having proper referral strategies being a, and these people being educated, the other providers that you mentioned. Yep, absolutely.

Dr. Christopher Ritchlin:
I think that in England also, correct me if I'm wrong Atul, that physiotherapists have been very much involved in some of the referrals and that's proven to be very successful. Correct?

Dr. Atul Deodhar:
Great point and also in Canada. So this is now, I don't know in all over Britain, but certainly in areas where there are people in Bath is very, you're talking about where, of course the ankylosing spondylitis was being researched for a very long time, physical therapists or physiotherapists, and also in Canada, because that's again where the patients go and that's where the physiotherapists can get the history and if the history is of inflammatory back pain, again, inflammatory back pain is not a disease; inflammatory back pain is just a symptom. Only 15% of people who have inflammatory back pain would have axial SpA. Having said that, that should really, really make them think maybe there's something else going on like our 44-year-old gentleman. He had classical, it was waking him at night in his twenties and thirties, great response to nonsteroidal, exercise would get it better, rest would get it worse. I mean, this is so classic. I mean, you know, that's the time when they should have sent him to see if, is really because of his running and jogging or is something else going on. And that's what has been taught to physical therapists that has been taught to chiropractors and a physiatrist, et cetera.

Dr. Alexis Ogdie-Beatty:
I was just to throw out there too, that I think it's not always that they're being misdiagnosed by non-rheumatology providers. Sometimes

actually rheumatologists are missing the diagnosis or saying this is probably related to other things going on. And one of the things that I see a lot is that people are getting lumbar spine films and then stopping and saying, “there's nothing there so you don't have ankylosing spondylitis,” not doing any workup that pelvis for example.

Dr. Atul Deodhar:
Alexis, you make a great point because the PROSpA study, in which that was a study where patients were referred to rheumatologists with a suspicion of axial SpA, and we were supposed to do the investigation and say, which people have axial SpA, which don’t, in which we found out there is this 14 years delay. In that study, nearly half of the patients, 47% of the patients we found, well, in fact, the rheumatologists existing practice, these people were in the rheumatologists practice for years being misdiagnosed. And they were just being followed by the rheumatologists for chronic back pain. And then I think that problem is getting less and less. SPARTAN and GRAPPA have done this, invest the symposia, which actually have educated rheumatologists. There are these more newer drugs coming into the market. Rheumatologists are awakening to idea of non-radiographic axial SpA. Rheumatologists are also awakening to the idea that it is more common in women. And that's my next case. If Chris will allow me, I'll tell you about that next case, which also brings to this point, how it is missed in women.

Chapter 5: Distinguishing Between nr-AxSpA and AS

Dr. Christopher Ritchlin:
So, yeah. So before we go there, I just like, when we comment on the patient case you just presented. How did you distinguish between non-radiographic axSpA or AS in that patient?

Dr. Atul Deodhar:
Yeah, so that distinction is very arbitrary. That distinction is purely dependent upon the x-ray of the sacroiliac joints.

Ankylosing spondylitis, to call somebody Ankylosing Spondylitis, they have to fulfill the modified New York criteria, which means they have to have at least bilateral grade 2 sacroiliitis or grade three or four or anything higher than that is AS. If they do not have bilateral grade 2 sacroiliitis, that becomes non-radiographic. What I want to say here very quickly is in day-to-day practice it does not really matter whether it is non-radiographic or ankylosing spondylitis. The treatment to me is very same and similar. Non-radiographic axial spondyloarthritis depends upon the sacroiliac joint inflammation as we see, or actually the post-inflammation. It's the sacroiliitis, the degree of sacroiliitis. And that is very subjective. If I see the x-ray and you see the x-ray, Chris or Phillip and Alexis, see the x-ray will between four of us will have multiple opinions. But to answer to your question, it is purely dependent upon the sacroiliitis level of that x-ray.

Dr. Christopher Ritchlin:
So let's go onto your next case, Atul.

Chapter 6: Case Review 2 – Imaging Considerations in AxSpA

Dr. Atul Deodhar:
Yeah. So the next case is also very interesting because this actually tells us what is happening now in women. Also the non-radiographic, since we're talking about that, non-radiographic axial SpA is as common in women as it is in men. Ankylosing spondylitis is more common in men suggesting that the progression from non-radiographic to radiographic is much more in men. So male sex is a risk factor.

This is a 34-year-old lady who was referred by the primary care physician for lupus. Right. She had hip pain, ankle pain, low back pain, all kinds of pain, pain, everywhere. And initially, they thought that this lady probably has fibromyalgia, but then as I will show in the next slide, her ANA was positive.

She visited Mexico in 2016, had dysentery, myalgia, fatigue, severe left buttock pain, again, left buttock pain, severe pain in buttocks, ankle, thoracic spine and chest. In the last four years, the chest pain was so severe that she actually went to the emergency room a couple of times, worrying that she had a heart attack. Cardiac workup was negative, and she was told that this is chest wall pain. This is not coming from your heart or your lungs. So, when the primary care doctor, of course, she had all kinds of aches and pain. She's a young woman, her ANA is positive one to 80, and she has got low titer anti-double stranded DNA positive. So, she was referred, to me, as lupus and generalized aches and pains.

And generally we tend to think these people, women, if there is nothing lupus related, this probably is fibromyalgia. All lupus connective tissue disease related history was negative, but she was excruciatingly tender on touching the rib cage. Iliac crest, this is a very interesting data that I found. Iliac crest is not generally tender in fibromyalgia ladies.

This is no synovitis, but there was something in the history and all of these started after their dysentery. I thought this could have been a

reactive arthritis type of situation, et cetera, plain x-ray as shown here is completely normal. Sacroiliac joints are very well-preserved and then I got an MRI done. These are two slices on the left hand, on the right. Two different slices. One after the other, she has badness, that's my radiologist said, she has badness on this x-ray. She has significant, not only there is significant bone marrow edema, but if you look on the left, actually the patient's right sacroiliac joint, and even the left sacral region, even on this, this is actually a STIR image. This is a fat-suppressed T2-weighted image. But even on this, you can actually see erosions in bilateral sacroiliac joints. She has significant erosion. She has got significant bilateral sacroiliitis. This is non-radiographic axial SpA because her plain x-ray is normal. That x-ray that I showed you doesn't show any grade 2 sacroiliitis.

And here is the point that in women, they have been missed as fibromyalgia. They have been called all kinds of stuff, but the history was of that of enthesitis everywhere. And all of this started after dysentery and this rib cage pain and this pain, I mean, generally women don't go to the emergency room with fibromyalgia for their chest pain and all this kind of stuff.

So this was another thing. Opening our eyes, that it is also common in women. We shouldn't be missing this.

Dr. Christopher Ritchlin:
Thank you, Atul.

Chapter 7: Imaging Modalities in the Evaluation of Axial Disease

Dr. Christopher Ritchlin:
I'm going to turn to Philip now. What are the different imaging modalities available to evaluate axial disease and distinguished between the two types of axSpA?

Dr. Philip Mease:
Atul has addressed this already. And, just to reiterate, we typically start with x-ray evaluation because radiography units are ubiquitous and they're less expensive. It's easier to obtain a problem. That was pointed out by Alexis is that typically a patient will come into me and they'll have had three different sets of lumbar spine films, but no evaluation of the pelvis and the sacroiliac joints per se. And, especially when we're starting to get into patients as they age a bit, we've missed the diagnosis for a while. They they're in their forties or fifties. You can start to see degenerative changes on x-ray of the lumbar spine to easily attribute the back pain to that.

So a key is to start with a radiograph. In my ex practice, if we have a normal appearing pelvis, the sacroiliac joints look normal or nearly normal. We're not seeing a pathology necessarily in the hips or the synthesis pubis. And we will move on to obtaining an MRI scan and MRI gives us much more detail, much more ability to tell about current active inflammation as well as damage. X-rays really are primarily to show us evidence of prior inflammation and now current damage. Sometimes CT scans can be done. Historically we've shied away from them because of the amount of radiation exposure involved but, there's been a move to using low dose CT scanning as a way of telling about bone damage as well as diagnostic purposes. But I would say the major ones are x-ray and MRI. And this gives us a bit more detail about what we've just been talking about.

We know that, especially at the very beginning of the development of axial spondyloarthritis, often times the patients will have negative x-rays of their sacroiliac joints. There just hasn't been enough time and inflammation for damage to occur. So it's incorrect to assume that all patients, who are quote non-radiographic, are eventually going to become ankylosing spondylitis, that's not the case.

As we track the disease over time, we will see increasing evidence of sacroiliac joint changes on x-ray, and then also here, we're seeing evidence of MRI inflammation. So let's look at these images. If we focus in on C for example to start with, this corresponds to the patient that Atul just showed us, with dramatic light up in the bone adjacent to the sacroiliac joints and some erosive change as well. In image B, we're not showing that kind of change. And then in D and E, we're seeing some of the radiographic changes with the sacroiliac joints on both sides showing periarticular sclerosis, some joint space narrowing as well as some erosive change. And then on lateral view of the lumbar spine we're seeing syndesmophyte formation, bridging the vertebral bodies.

Here we're seeing a higher power or view of what we are looking at in the x-rays. So, starting with the sacroiliac joints, we see significant periarticular sclerosis, joint space narrowing, in fact, almost complete loss of joint space. This is considered grade three, grade four would be ankylosis of the sacroiliac joints.

And if we move our eye to the spine image, we're seeing evidence of syndesmophyte formation, bridging the vertebral bodies and this person is almost appearing as the classic bamboo spine change. There's also something known as shiny corners. We would look for that on the lateral view of the lumbar spine, where at the annulus for the intervertebral disc right at the corner of the vertebral body, we'll see light up which looks shiny and then would be enthesitis.

Moving on to MRI scanning. If, as I mentioned earlier, if the SI joints were normal on x-ray, if we have a high suspicion for this representing an inflammatory immunologic problem, if the patient is endorsing inflammatory back pain criteria such as, waking up in the

middle of the night with pain or a pain getting better with activity and worse with rest, then we order an MRI scan.

Note that contrast is not necessary for this particular image. And what we're seeing here is evidence of inflammatory light up in the bone, adjacent to the sacroiliac joint, which is consistent with lymphocytic infiltration in these areas.

So, that is seen in both images, B and C and with more dramatic changes, I noted on the patient's left with the erosive changes as well.

And so we're looking for evidence of both damage and inflammation when we're looking at the MRI scan.

Chapter 8: Pitfalls in Interpreting MRI Results for Axial Disease

Dr. Christopher Ritchlin:
Philip, thanks for a great summary of the radiographic and imaging findings in axial SpA. I'm going to turn to Alexis now, what are some of the pitfalls in interpreting MRI results? Overall, how can rheumatologists better assess patients with axial disease?

Dr. Alexis Ogdie-Beatty:
Great question. So, just as we talked about how we can miss the axial symptoms or axial disease by not imaging the right place, sometimes we can also over-interpret what's actually in front of us. So, actually before we even get to MRI on plain films, one of the things that I sometimes see is people being called ankylosing spondylitis when they actually have DISH, and then that might point you to a different diagnosis too. So, in terms of over over-interpreting, sometimes those flowing candle wax, syndesmophyte looking things can be DISH. So, something to also consider.

And then within the MRIs, it's interesting because actually even healthy individuals can have bone marrow edema, much less common erosions, but bone marrow edema can be seen in healthy individuals.

In particular, this is going to be in healthy individuals who have some other risk factor. And I'm going to talk about a couple of those risk factors. So, one of the key risk factors is actually marathon running or hockey playing, or even just actual recreational runners.

So, in one really cool study that they did among hockey players and then a separate study among recreational runners, they found that 30 to 40% of them actually had sacroiliac joint inflammation that looked like bone marrow edema, consistent with what you might call non-radiographic axial SpA. So, I think that's just a cautionary tale. So, we have our patient with back pain. We don't want to get MRIs of the sacroiliac joint in every patient with back pain.

It really should be someone who has inflammatory back pain and kind of symptoms consistent with the diagnosis. So, you want to think about what is the positive predictive value in this individual? And how's this task going to change the likelihood that the patient actually has the disease? So, here in this particular image, you can see some of that similar bone marrow edema as shown in the previous slides by Phillip. And then the subsequent side, one of the things that we see often as well is if you're going to get an MRI of a pelvis in a postpartum woman who has back pain, a common clinical scenario, you may also find bone marrow edema that looks similar to non-radiographic axSpA. So I've actually seen a couple of these in my practice as well. Patients who are six months out from having their baby and they've gotten an MRI of the pelvis because they're HLA-B27 positive potentially or have something else that goes along with the disease. So, they got the MRI and it's positive. So, then the question is, what do you do with that bone marrow edema?

Well, in up to 46% of women with pregnancy-related low back pain in one study actually had similar changes. So, bone marrow edema, sclerosis, and they even saw some erosions. But again, erosions are still going to point you more in the direction of axSpA or erosions are less common in that healthy individual, as opposed to the bone marrow edema. And there's studies that suggest that this sticks around for up to 12, nine to 12 months, some studies have suggested it lasts even further.

So it had to be cautious in that postpartum woman who you're ordering an MRI of the pelvis for.

Dr. Atul Deodhar:
Chris, can I jump in; just a quick one here? I mean, the other thing that will happen, of course, in some postpartum women is on plain x-ray of their sacroiliac joints, they can have this osteitis condensans ilii.

That's another thing. I mean, apart from DISH on plain x-ray being confused with ankylosing spondylitis, postpartum women, or those who have actually had multiple births. They actually can have these triangular sclerosis on the iliac side, lower quadrant of the sacroiliac joint, and that sometimes is missed for sacroiliitis.

And again, as Alexis said, the erosions are the ones which kind of generally differentiate in general between the patient who has got an immune-mediated destructive inflammatory lesion versus these kinds of non-immune mediated things. And in our 44-year-old gentleman that I said he was an athlete.

And we also considered, and his MRI was done actually probably four or five months after that Ironman Canada problem or not problem,

the race that he ran, but he had erosions, he had definite erosions and that kind of clinch the diagnosis that this is not just related to that. And it had lasted for 18 months. So, thank you, Alexis. This is the structural damage, which kind of changes the dynamic, whether this is really a pathologic or this is physiologic inflammation. One last quick point is that the ASAS MRI group is coming up with new definitions. And in this American College of Rheumatology Annual Meeting, there are presentations related to that poster and oral presentations about this definition is changing.

What is positive MRI? Those definitions are changing and I would suggest our viewers to look specifically for how these definitions are changing.

Dr. Alexis Ogdie-Beatty:
Right. And so you pointed out some really good points, which are osteitis condensans-I forgot to mention that. But, also that it's not easy to define a positive MRI. And so it's critical to look at it yourself. So one of the things that, one of the questions that Chris originally had was what do you kind of make of this? Or how do you put this together in terms of making a diagnosis? And one of the things I try to do is always look at the sacroiliac joint x-rays myself.

If I'm not sure, and especially when there's osteitis condensans called in a patient who you think could have axial SpA, I talk with a radiologist at the very least and make sure that they really think that's what it is given this particular clinical scenario. And finally, MRIs, also looking at the MRIs yourselves, because it's not too hard once you kind of get a general idea of what you're looking for.

Walter Maksymowych has that website CaRE Arthritis, where you can do all kinds of modules to learn how to read MRIs. And I found that very helpful in terms of being comfortable looking at them myself.

Dr. Atul Deodhar:
Yep. Yep. Great point.

Dr. Christopher Ritchlin:
Thank you. Thank you, Alexis and Atul. It was a great discussion.

Chapter 9: Case Review 3 – Diagnostic Delays in AxPsA

Dr. Christopher Ritchlin:
I'm going to turn to Philip now and ask him to share a case of a patient who experienced a delay in diagnosis of axial PsA. What clinical and imaging features did the patient present with?

Dr. Philip Mease:
Thanks, Chris. This is a 45-year-old woman who has had psoriasis since her mid-thirties. She had some peripheral manifestations, suggestive of psoriatic arthritis diagnosed in her mid-forties and she has been managing the psoriasis with topical agents or light therapy and she's been managing the psoriatic arthritis symptoms with nonsteroidal anti-inflammatories. Interestingly throughout all of this, she's had ongoing back pain. This was something that she just simply attributed to gradually getting older. And she had never brought it up with her dermatologist who never asked her about it. Then eventually, she went to an orthopedist and a lumbar spine was done which identified degenerative changes, not too surprisingly. And then, what happened is that her back pain was attributed to these degenerative changes. However, eventually the dermatologist and she said, well maybe we should get a evaluation by rheumatology. So, they referred her over to their local friendly rheumatologist and we did much of the workup that we've just been walking through. That is obtaining an x-ray of the pelvis which was unremarkable in the sacroiliac joints and then moving on to more advanced imaging, including MRI, to finally assess the fact that there was inflammation consistent with axial psoriatic arthritis.

Dr. Christopher Ritchlin:
So, thank you, Philip. Alexis, how common is axial PsA and why do patients experience a delay in diagnosis of their axial involvement?

Dr. Alexis Ogdie-Beatty:
Great question. So first, the estimates vary and it depends on how you define axPsA, which we're going to get to in a little bit, is a challenging aspect in and of itself.

But one study within Corrona suggested about 12 and a half percent of patients with psoriatic arthritis have either a diagnosis of axPsA by imaging or by the clinician saying that they have axPsA. There's a quote that two to 5% of patients with psoriatic arthritis have axial disease only. I think that group of patients is a difficult group of patients in and of itself because sometimes they're called axSpA with psoriasis. So, that's difficult to know what you can say what proportion, but how many of those patients differs and about how they're called. And then one of the interesting studies from Canada suggested that 15% of patients who didn't have axPsA at baseline developed the disease over the course of the 10 years in their axial joints.

So, why is it that we're not catching this right away or why might it be that we're under capturing axial disease? Well, number one is that there's not a great definition for axial PsA, as we just mentioned and we'll talk about that in a little bit. Number two is that patients may not have symptomatic axial disease. Up to half of patients with axial PsA aren't really bothered by their axial symptoms so, that's not what they're coming to you for. They're coming too often because they have swollen joints that are painful, or they're just kind of having lots of areas of pain and that's not really the key area for them. So, you're kind of going with what you're treating their current symptoms that they're telling you about, maybe not knowing that they have axial symptoms. So, I think there's a lot to think about in terms of how we should go about identifying axial PsA. And one of the ways to do that is just to get imaging for everybody; the axial of the sacroiliac joints, for example. But then, you know, there's discussion about resource utilization stuff there. So I think this is still a challenging area.

Dr. Christopher Ritchlin:
Alexis, how has axial PsA clinically differentiated from axial disease and axSpA?

Dr. Alexis Ogdie-Beatty:
This is a great question. And Philip and I have been kind of discussing this as well as in some of our work together. The question is, is it different? And we don't really know very well if it's different, there's some little features here and there that are different.

They have a lot of overlapping features. So, if you just take axSpA and PsA, a group of patients with axSpA and a group of patients with PsA, and follow them over time you see that a good proportion of each group fulfills the criteria for the other groups. So, let's say about 20% in each group. So, they truly are kind of overlapping circles and a Venn diagram. And back to you, Chris.

Dr. Christopher Ritchlin:
Thanks, Alexis.

Chapter 10: Distinguishing Between AxSpA and AxPsA

Dr. Christopher Ritchlin:
This next question is for Philip. How are demographic genetic clinical and imaging features different between axSpA and axial PsA?

Dr. Philip Mease:
So Chris, this has become quite an interesting and focused topic in the last short while, because we're beginning to see that there are meaningful differences, but as Alexis has mentioned a considerable overlap as well, and let's walk through some of these. So, for example, we know that patients who present with axial PsA present a bit later in their disease. So, unlike the radiographic axial SpA patient or ankylosing spondylitis patient who presents as a younger male in their late twenties, mid to late twenties, we're seeing PsA patients have their peripheral manifestations of PsA begin initially and then later on in their late thirties, forties, they are developing their axial PsA manifestations at a time like our patient that we just walked through where you get confused and attribute her symptoms to degenerative arthritis in the spine. And it's not until we see the characteristic MRI changes of axial PsA that we ended up moving her on to effective therapy, effective biologic therapy, which made such a huge difference to her. She's also characteristic in that she's female. And we see that in axial PsA is more likely going to be either equal numbers of males and females or more females involved as compared to ankylosing spondylitis, which is predominantly male.

Genetics are different. We know that for example, HLA-B27 is about four times less likely to be positive in an axial PsA population than an ankylosing spondylitis patient. The latter you should be see more than 80%. The former, we typically see somewhere around 20 to 30%, depending upon the cohort being B27 positive.

But that also opens the door to some other interesting observations. For example, the group from Dublin working together with Bob Winchester in New York, identified that there were a number of patients who were HLA-B08 positive and they had an interesting feature of asymmetric sacroiliitis if they had sacroiliitis. So, one side might be quite involved and the other side not at all. There are a number of clinical features that are quite different. The patients with psoriatic arthritis may actually not even present with back pain. They may be asymptomatic despite showing imaging evidence of a spondylitis condition.

They also tend to have better movement capabilities. So, when you do measures of spine mobility, they're less involved or less severe than the patients with ankylosing spondylitis and in a similar way, when we apply various axial disease activity scores, like BASDAI for example, we find that the patients, with axial PsA may be a bit better.

The physicians consider that the same. They often are less likely to be treated with biologics, even though they could well benefit from them. They tend to have more evidence of peripheral arthritis in patients with ankylosing spondylitis. But, they do have a similar prevalence of enthesitis.

And when we look on x-rays or imaging of the pelvis area, we find that generally the sacroiliac joints may not be as involved. They may end up being grade one or two, they may be asymmetric with one side being involved and the other not, or they may not be involved at

all. There's a substantial cohort of axial PsA patients who have completely normal SI joints, but their spine may be involved including their cervical spine.

Here are some imaging differences to point out between patients with axial PsA and axial spondyloarthritis. On the left, we're seeing a patient with asymmetric sacroiliitis where on this patient's right it is a grade two change and on the left, it's a grade four change, meaning it's ankylosed.

When we look at the spine, we see some, what are called chunky, non-marginal syndesmophytes forming and they are not as symmetric as we tend to see in classic radiographic axial spondyloarthritis. There may be some parts of the vertebral column that are involved and others that are not at all involved.

And we also see more frequent fusion of cervical facet joints. So, I can think of several patients in my practice where they have very prominent cervical disease, but much less in the way of lumbar or no sacroiliac involvement. And on the axial spondyloarthritis side, we tend to see more symmetry between the sacroiliac joints. And this is associated with B27 positivity. The sacroiliitis tends to be worse. And then you see the characteristic marginal syndesmophytes that are ossifying the vertebral column and this characteristic bamboo spine change.

Atul, what are your thoughts on this?

Dr. Atul Deodhar:
Yeah, thanks Phillip. So, most of these things you have covered already.I will start from the cervical spine and then go further down. Phillip already mentioned is-I have patients with psoriatic arthritis who have axial involvement, and Phillip already said completely normal sacroiliac joint, but they have involvement of their cervical spine.

And this is not uncommon. That could be an isolated involvement in patients with axial PsA, so a psoriatic arthritis patient complaining of neck pain, we should look at x-rays of their cervical spine because you might actually find a chunky syndesmophyte there. And one of the things which Alexis mentioned earlier, also, was that this kind of happens a little bit later. I mean, in the early stages and patients have multiple peripheral symptoms and psoriatic arthritis we are also more sort of concerned about their MCP joint and PIP joints and DIP joints and ankles and knees and enthesitis. We forget to ask them about the axial skeleton, and this could be one of the major involvements which can affect their quality of life quite adversely. So, starting from the top as shown here in this figure in the cervical spine, there is more frequent cervical spine involvement may be isolated in axial PsA; very, very rare in axial SpA. Phillip has already said about the chunky syndesmophytes and paravertebral ossification and asymmetric syndesmophytes in axial PsA. In the thoracic spine of axial SpA, there is marginal syndesmophytes, they are symmetric and these are kind of very nice and not chunky. If you look at the lumbar spine, there is more frequent fusion of facet joints and HLA-B27 involvement, HLA-B27 will be positive. In about 90% of the patients who are axial SpA. In axial PsA again, HLA-B27 is less common, syndesmophytes may again occur in the absence of sacroiliitis. And then the sacroiliac joints themselves axial SpA would have more symmetric, more severe. Whereas an axial PsA, it will be less symmetric, it will be more asymmetric and, this point has been made already, that HLA-B08 this particular genotype in psoriatic arthritis, patients have asymmetric sacroiliitis rather than symmetric sacroiliitis. The inflammatory, going back to in fact presentation, inflammatory back pain that I spoke about earlier, inflammatory back pain is less common, interestingly in axial PsA, their back pain might sound mechanical. So, that inflammatory back pain, the way the patient expresses their back pain and the way you understand it. So, lower frequency of inflammatory back pain, older age at presentation, and generally the presentation is peripheral more and then, axial the later part of their psoriatic arthritis career, they have more axial involvement. Whereas of course, in axial SpA, it's younger age, we already covered that also earlier. Chris?

Dr. Christopher Ritchlin:
Alexis, a consensus definition is currently under development in psoriatic arthritis. What do the members of ASAS/GRAPPA considered to be the most distinguishing features of axial PSA?

Dr. Alexis Ogdie-Beatty:
Great question. So, a few years ago, GRAPPA and ASAS, both recognized the definition of axPsA needs to be defined and there needs to be consensus on what is this definition so that we can better understand the epidemiology and better identify axial PsA.

So, they've been working together over the last couple years to develop these definitions through prospective cohort studies and a variety of other imaging studies, for example. So, it is still under development. But the preliminary thoughts about an axial PsA definition are that it would include imaging and we're still waiting to figure out what those imaging features are.

They're most specific and most helpful for this diagnosis and then a definition for back pain. So, that's again, something that they're working on. So, there's probably going to be two components of this in the setting of a defined PsA.

Dr. Christopher Ritchlin:
Great. Thank you, Alexis.

Dr. Philip Mease:
So Chris, if I could just add, we're very excited about this project going forward. It's, a wonderful example of a collaboration between two organizations. I've had great coordination with Dennis Poddubnyy and Désirée van der Heijde and so on as we are beginning to, or about to launch, in this next year, this study of probably it will end up being over 400 patients where we carefully identify and then come up with a classification criteria for axial PsA, which I think is going to be so important as we move forward into doing studies specific for those patients.

Dr. Christopher Ritchlin:
Great point. Thanks, Phillip. So, this has been a really marvelous discussion and to summarize, IL-23 dependent and independent sources of IL-17, play a key role in both axial PsA and axial SpA. Axial involvement is an important feature of both axSpA and axPsA, and imaging is an essential component of assessing axSpA and axPsA.

Patients with axial involvement may experience a delay in rheumatology consultation and diagnosis. Axial disease and axSpA and axPsA share various similarities and differences. Consensus definition of axPsA is anticipated. There are common features in spot patients with axial disease. Early recognition is crucial to improve outcomes and quality of life in patients.

Well that again, I want to thank the speakers tonight and I want to thank you for your attention.

Dr. Atul Deodhar:
Thank you. Thanks. Thank you.

Announcer:
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