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Unveiling AOSD: Connecting the Dots in the Spectrum of Still's Disease

Chapter 1: Recognizing Systemic Juvenile Inflammatory Arthritis and Adult-Onset Still's Disease

Announcer:
Welcome to ReachMD. This Medical Industry Feature titled, Unveiling AOSD: Connecting the Dots in the Spectrum of Still's Disease, is sponsored by Novartis Medical Affairs.

Dr. Christopher Ritchlin:
Good evening and welcome to tonight's program. Tonight, we are going to discuss "Adult-Onset Still's Disease Unveiled: Connecting the Dots on the Spectrum of Still's Disease". We are going to have a collaborative discussion to better understand and expedite the patient journey. I'm Christopher Ritchlin from the University of Rochester Medical Center. And I'm located in Rochester, New York.

And the 2 speakers who are with me tonight are actually in New York City and due to technologies and great advances in technology we're all going to be on the same stage for you.

My first speaker is a Petros Efthimiou who is from the New York Rheumatology Care in Manhattan, New York and Olga Petryna who is from the NYU Langone Medical Center.

This slide shows the disclosures and it's important to point out, this presentation is sponsored by Novartis Pharmaceuticals Corporation and all speakers have been compensated for their time. The disclosures for each speaker are listed here.

Considering the new insights on Still's disease in your medical opinion, Dr. Efthimiou, do you recognize systemic juvenile inflammatory arthritis and adult-onset Still's disease as part of the same disease continuum?

Dr. Petros Efthimiou:
Yes, Chris, I think they're a part of the same continuum, obviously with different agents. They share cardinal features such as the spiking fevers, the arthritis, the evanescent rash, and also the leukocytosis or neutrophilia, that's often seen in both conditions. The patients with both conditions are also predisposed for life-threatening complications, such as the macrophage activation syndrome, which is particularly common in both conditions.

We also observed frequently serologic markers of inflammation that are very elevated such as the erythrocyte sedimentation rate, the C-reactive protein, and the often the serum ferritin.

So both conditions have a different presentation sometimes, but they're minor differences. So there are a lot more commonalities than differences in those conditions. For example, they have been reported a slight preponderance of female patients with the adult form of the disease.

Also, prodromes, like the sore throat tends, to be more frequent or reported more frequently in patients with the adult form of the disease. Additionally, arthritis of the lower limbs and the ankles seems to be a little more common in kids.

Of course, the underlying pathophysiology tends to be very, very similar if not identical. And there seems to be an imbalance between proinflammatory cytokines and anti-inflammatory cytokines or mechanists to resolve the systemic inflammation. If this pathogenic model of systemic JIA and adult Still's disease, there seems to be a pivotal pro-inflammatory cytokine, which is interleukin 1.

It plays a role in both innate and adaptive immunity and defines the biological evolution of arthritis in systemic JIA and Still's disease. How does it do that? Well, in the looking around promotes inflammation in an antigen independent manner through activation of the endothelium, leukocytes and resident tissue lineages. It also modulates antigen driven T-cell immunity by activating T cells and inhibiting

the efficacy of regulatory T cells and also promoting T helper 17 cell differentiation.

Nuancing the SJIA is characterized by excess IL-1 production, and that could rise to give the clinical presentation of inflammatory arthritis.

In this slide, we see the molecular players of adult-onset Still's disease pathogenesis, and you will notice the similarities to the previous slides regarding systemic JIA. Against dangerous signals like PAMPs, pathogen- associated molecular patterns, and damage associated molecular patterns can trigger innate immunity through the activation of toll-like receptors and the activation of the NLRP3 inflammasome. We also know the successive activation of NLRP3 a that leads to the intense production of the interleukin 1 beta and interleukin 18. They're both members of the interleukin one super family.

So the cytokines intensely stimulate the innate immune cell activation as well as adaptive immune cells and leads to over production of several pro-inflammatory cytokines that included the interleukin 6, interleukin 8, interleukin 17 as well as tumor necrosis factor that drives further the production of interleukin 18 in an autocrine pattern. Several factors actively contribute to amplify the inflammatory response, which is often referred to as cytokine burst or cytokine store. In addition to interleukin 1 beta confer retrograde activation of macrophages and neutrophils alarming such as the S100 proteins and advanced glycation end products or AGEs are involved. Deficiency or failure in regulatory or anti-inflammatory mechanism may be involved in the pathogenesis of inflammatory diseases include deficiency of regular regulatory T cells.

So in this study of patients with adult Still's disease and SJIA, we see a similar patterns of different cytokines. For example, we see elevating interleukin 18 as a common feature in both active phase adult-onset Still's disease and SJIA. We also know the significant increases in the serum neopterin interleukin 18, soluble tumor necrosis factor receptor type 1, and also soluble tumor necrosis factor type 2 that were observed both in the macrophage activation syndrome phases of both disease. Interleukin 18 remained elevated during the inactive phases of both diseases, whereas other cytokines that were elevated during the active phases, normalized once patients achieved clinical remission.

Chapter 2: Clinical Features of SJIA and AOSD

Dr. Olga Petryna:
When it comes to clinical features in patients with systemic JIA and adult-onset Still's disease results from the retrospective medical records study of adult and pediatric patients showed certain differences and similarities in the presentation of the disease clinically. For adult patients, the frequency of fever, skin rash, myalgia, weight loss and sore throat were significantly higher when compared to patients with juvenile-onset disease. When it comes to the significant differences in patterns of the fever, skin, rash, or localization of the rash, there was no difference between the groups.

Results from the retrospective medical record study of adult and pediatric patients with Still's disease identified certain similarities and differences in laboratory features of the patients. Liver dysfunction, as well as neutrophilia were more common for adult patients. Also, on comparison of the bone marrow, higher rate of granulocytic hyperplasia and hypercellularity of the bone marrow were typical for patients with adult-onset Still's disease.

There is no differences observed in radiological findings between the 2 groups.

A retrospective analysis of medical records study of adults and pediatric patients with Still's disease identify similarities and differences in the articular features of the patients.

Most commonly affected joints for adult patients were wrists, knees, and ankles; when it comes to the pediatric cases, ankles and knees seem to be more common comparing to wrist and elbow and metatarsal phalangeal joints. Hip and cervical joints followed amongst the most prevalent in pediatric cases.

Skin rash is a characteristic feature of adult and pediatric cases with Still's disease. On the left, you see a picture of the skin rash, which is a maculopapular rash, typical for a pediatric case where the linear streaks where skin was scratched so-called Koebner phenomenon. On the right figure, you can see a salmon-colored, nonpruritic maculopapular rash that is common for adult-onset cases.

Joint damage is a common feature of Still's disease and may lead to erosions and ankylosis. The left image shows an x-ray of a 15-year-old girl with systemic juvenile idiopathic arthritis, experiencing rapid progression of joint space loss, erosions, and subsequent ankylosis of both wrists, despite the treatment received. On the right, you see an image of an x-ray of patients with adult-onset Still's disease, with a distinctive pattern of intercarpal and carpometacarpal joint space narrowing that can lead to ankylosis.

What I often observe in my practice is that of the patients who get diagnosed earlier in life tend to have more progressive and aggressive debilitating disease with more evidence of erosion and ankylosis going forward, despite the treatments they receive. I'm

wondering if, Petros you share the same experience with your patients where older patients tend to have milder disease if their onset is later in life?

Dr. Petros Efthimiou:
Thank you, Olga. Indeed, my experience is very similar to yours. And, again, I notice all the time that there can be a delay in the diagnosis of adult Still's disease, where our friends the pediatric rheumatologists, are very good and very fast and make the diagnosis of SJIA.

The reason I'm saying this to you is because if we wait too long, then we're going to notice the complications. That could be irreversible joint damage and wrist ankylosis. It could be the ever feared and life-threatening macrophage activation syndrome. So I believe that making the diagnosis of SJIA and AOSD is an urgency. It's a medical emergency and the faster we make the diagnosis, the better outcome the patients will have. One thing I always say to my colleagues is that the arbitrary age of 16 is something that is a little bit official, because if the patient has the first manifestation of symptoms, at the age of 16 or older, then we call it the AOSD.

While the patient had the earlier onset of symptoms, before the age of 16, we call it the SJIA. It's common that I will ask the patient and sometimes the patient's family about childhood illnesses or childhood hospitalizations with fever or an unknown infection because that can often help us make the accurate diagnosis distinction. Chris?

Chapter 3: Case Reviews – Features and Diagnosis of AOSD

Dr. Christopher Ritchlin:
Yeah. Thank you, Petros and Olga for a great discussion. I was wondering if, Olga, you can share a case of a patient who was diagnosed with AOSD and what were the features that the patient presented with?

Dr. Olga Petryna:
An example of such case would be a 29-year-old Caucasian male software engineer who presented with symptoms that started about 2 months ago and the most prominent centers of his case where quotidian fever up to 102 Fahrenheit, which typically happened in late afternoon towards the end of the day associated with the erythematous rash cover and his torso and thighs. He also experienced painful and swollen wrists, increased level of fatigue, and enlarged lymph nodes on his neck.

When the biopsy of the lymph node was performed, it shows signs of reactive lymphadenopathy.

When it comes to his medical history, he has no known prior medical conditions, no childhood illnesses or hospitalizations.

He had a sore throat for 3 months prior to the current presentation and his strep throat test was negative at the time of initial presentation. He was given lozenges, several courses of antibiotics and antihistamines with no resolution of the sore throat. He had unremarkable family history, no recent travels, he did not use any recreational drugs, did not smoke and socially drank only.

In terms of clinical and laboratory results, his results were notable for elevated sedimentation rate, high CRP levels, leukocytosis, elevated AST and ALT as well as serum ferritin levels of 12,000. His serum D-dimer was high at 1.1. CT angiogram was negative for blood clots and transthoracic echocardiogram was normal.

His autoimmune serologies, such as rheumatoid factor, CCP, ETA 14-3-3 were all negative as well as ANA panel, SSA and SSB were normal. On your analysis, there is no abnormal findings, as well as blood and urine culture were normal at the time.

Dr. Christopher Ritchlin:
Thank you, Olga. Petros, what are the criteria to diagnose adult-onset Still's disease?

Dr. Petros Efthimiou:
Well, Chris, there are several sets of criteria that are validated and can help us classify patients as having adult-onset Still's disease.

Interestingly, the main set of criteria described by Dr. Yamaguchi and associates, is still the most commonly used set of criteria. It has a sensitivity of 96% and a specificity of 92%. It requires the exclusion of infectious, malignant, and autoimmune conditions before it can be applied. So basically it's a point system you need to have at least 5 or more points to make the classification of adult Still's disease.

Some of the major criteria used is the fever has to be more than 39 degrees Celsius, lasting at least a week, arthralgia lasting at least 2 weeks, the typical rash that Dr. Petryna showed before as well as leukocytosis with a numbers above 10,000 white blood cells per cubic millimeter. The minor criteria include the sore throat prodrome, lymphadenopathy or splenomegaly, the liver dysfunction, and the negative rheumatoid factor and the ANA. They're also the criteria proposed by Dr. Jack Cush and Dr. Bruna Fautrel in Paris. That includes additionally serologic markers that we previously described.

Dr. Christopher Ritchlin:

Thank you, Petros. Can you share a case of a patient with adult-onset Still's disease who experience a slowed diagnostic journey? What barriers did you and the patient encounter?

Dr. Petros Efthimiou:
Absolutely. It's actually a case that I saw last month in September. So a very pleasant, 19-year-old, Caucasian female. She's a college student in New Jersey. Both her parents are dentists that were very concerned about her. The symptoms started 14 months ago and there were still no diagnosis made. There was repeated focus in ruling out Lyme disease, which is prevalent in New Jersey, but her presentation was very suspicious for adult Still's disease.

She had quotidian fevers more than 102 degrees Fahrenheit. She had the erythematous rash covering the chest, back, upper shoulders and upper thighs, painful, swollen wrist. I remember her saying that she couldn't type and she was falling behind her college schoolwork. And she was severely fatigued, unable to focus on her studies or do the things she liked to do with her family.

Her medical history was unremarkable, no childhood illnesses, no hospitalizations. Nothing in her family history. She admitted reluctantly to mild alcohol intake.

And it's interesting that over the last 14 months, she received several courses of antibiotics, both oral and intravenous in the hospital because her physician was convinced that it was difficult to diagnose Lyme disease. However, all tests for Lyme came back negative.

Her laboratory markers were quite telling of systemic inflammation, it's got the high SED rate, high C-reactive protein, white cell count of 13,000, elevated transaminases, serum ferritin of 9,000 and also high D-dimer of 0.9 micrograms per ML. All her autoimmune tests, including rheumatoid factor, ANA, CCP were negative.

And the initial workup shows no evidence of mononucleosis. Of course, she underwent the very extensive infectious workup that was testing her for Lyme, Babesia, Erlichia and her blood cultures were unremarkable as well as a urinanalysis.

What was quite disheartening was her x-ray, x-ray of the hands of the wrist that showed advanced disease. I'm showing here in the x-ray the ankylosis that started happening in her wrists was the periarticular osteopenia, the loss of bone lines and severe arthritis. So unfortunately for this young lady, the damage was done and that's irreparable.

Chapter 4: What Are the Criteria to Diagnose AOSD?

Dr. Christopher Ritchlin:
Thank you. Olga and Petros, one of the things I've noticed in our hospital is that these patients come in and they're, as you just told us, they're treated with antibiotics by multiple different from all of the different presumed problems and we're not called until much later. And usually we're called in after they find that the ferritin is severely elevated. Have you 2 had similar experiences like that?

Dr. Olga Petryna:
Well, elevation of ferritin levels is one of the diagnostic features typical for adult Still's disease but it's not always the case for all the patients. It still is a quite nonspecific inflammatory marker, which can be seen in other conditions in quite higher levels, above a thousand. On the other hand, there are plenty of patients without adult-onset Still's disease who present with fairly low or close to normal ferritin levels.

In my opinion, it should not be used as the only marker for diagnosis. And it's a complex condition that requires multiple features combined together to make the diagnosis.

Dr. Christopher Ritchlin:
Has that been your experience as well, Petros?

Dr. Petros Efthimiou:
Absolutely. So I think serum ferritin can be useful when elevated, but the absence of elevated ferritin should not exclude adult Still's disease.

Dr. Christopher Ritchlin:
Yeah, I totally agree.

Dr. Petros Efthimiou:
Yeah. And I often notice that there's a gap from the clinical presentation to the time that the serum ferritin becomes elevated. And if you just rely on serum ferritin, you're going to miss it, or are you going to delay treatment.

Dr. Christopher Ritchlin:
Yeah, I guess my point was it's often a trigger for a rheumatology consult from the medical specialties is interesting.

Chapter 5: Why Is Delayed Diagnosis an Ongoing Concern in AOSD?

Dr. Christopher Ritchlin:
I have a question for you, Olga. Why is delayed diagnosis a concern for patients with adult-onset Still's disease and what are the limitations, if any, of the classification criteria?

Dr. Olga Petryna:
Well, first of all, delay in diagnosis in patients with adult-onset Still's disease has been reported across multiple studies. And one of the reasons why the delay happens is the infrequency of the disease, as well as symptom heterogeneity in the absence of characteristics or serological findings, it oftentimes is difficult to come to the definite diagnosis. Also, the conditions require extensive exclusion workup to relay mimicking conditions as those can be also life-threatening and important not to miss. In patients with articular manifestations, a challenge presents when the arthritis presents early on with no evident erosion or ankylosis and without an ultrasound technique with simple x-ray, it's often difficult to diagnose inflammatory arthritis. A limitation of the classification criteria comes from the fact that it is based on the retrospective data, and they're not compared to a control group.

That leads to a significant delay in diagnosis in patients with different types of presentation of AOSD. On average report to delay in diagnosis is about 3 to 4 months, but it can vary significantly based on what type of manifestation they present with.

For example, patients with monocyclic disease can have a delay up to 12 months while patients with a chronic or polycyclic disease can be delayed in their diagnosis up to 20 years on average.

Dr. Christopher Ritchlin:
Thank you. Petros, what is a proposed diagnostic approach for adult-onset Still's disease? What strategies do you recommend to raise the index of suspicion and shorten the path of diagnosis of patients with adult-onset Still's disease?

Dr. Petros Efthimiou:
Absolutely Chris. So, I think it makes sense obviously to think about it and suspect it whether it's a process.

And, of course we have to go to a differential diagnosis and think about adult Still's disease, but we shouldn't forget that we should exclude infectious autoimmune and malignant etiologies before we make the diagnosis. So this is what the entails the extensive workup, but thinking about Still's disease and involving other specialties often leads to a prompt diagnosis and treatment. I think what's also quite helpful is the collaboration between pediatric and adult rheumatologists. Our friends, the pediatric rheumatologist, have extensive experience though systemic JIA. It can often help us with the diagnosis and it can also help us transition those patients when they become adults and have chronic Still's disease. So I'm showing here the diagnostic approach that can help the clinician make the diagnosis. So it involves obviously the workup involves exclusion of the other diseases, but there are a number of serologic markers that can help us for example, confirm the diagnosis and assess its severity. By no means that are diagnostic tests, but in conjunction with a clinical picture, they can help us make the diagnosis. Frequently people talk about the Still's triad, which is a typical presentation involving a high spiking fever, an evanescent rash and arthritis. But not all 3 conditions to be present at the same time to make the diagnosis.

Dr. Christopher Ritchlin:
So it's interesting that you mentioned that collaborating with our pediatric rheumatology colleagues. I wonder if this is similar to what happened in psoriatic arthritis, where the dermatologists and rheumatologists have started to come together. Do you think this is a kind of disease where we will see some collaboration between the adult and pediatric rheumatology community?

Dr. Petros Efthimiou:
I agree. I think it's a unique opportunity to bring together our colleagues, our pediatric colleagues and the adult rheumatologists that may know a little less about the autoinflammatory disease and systemic JIA. I think this continuum to be in everyone's mind, whether they're adult or pediatric rheumatologists and bringing our minds together will definitely help our patients get diagnosed promptly and be treated adequately.

Chapter 6: Case Discussion – Consequences of Delayed Diagnosis in AOSD

Dr. Christopher Ritchlin:
Petros, can you share a case of a patient who experienced a delay in diagnosis and how this affected their quality of life?

Dr. Petros Efthimiou:
Absolutely. I just presented previously that a case of the college student from New Jersey.

Remember, the 19-year-old girl had adult Still's disease because of diagnosis was made after the age of 16. That's the criteria for

diagnosing adult Still's disease versus SJIA. And if you remember from that case, the symptoms started 14 months ago. So there was valuable time that was lost before making the diagnosis that led to the patient's deterioration of her quality of life and unfortunately, led to the arthritis, destructive arthritis here raised that we can't undo right now. Had this patient been diagnosed earlier, we could have prevented a lot of the damage, but also the deterioration of her quality of life. She wasn't able to keep up with her college homework. She wasn't able to do her hobbies and spend time with family and friends. And this is 14 months that were actually wasted.

Dr. Christopher Ritchlin:
Thank you. Olga, we've just heard of a really terrible complication of disease from Petros' patient. What are the complications of Still's disease impacted by delay diagnosis and failure to control disease activity?

Dr. Olga Petryna:
So, despite the life-threatening complications that I mentioned before, macrophage activation syndrome, amyloidosis and joint erosions, we also need to keep in mind that the disease puts significant burden on patient's life, which leads to a lot of uncertainty around the flare ups, fatigue, physical disability and inability to participate in their day-to-day life. That leads to a poor quality of life and ability to perform properly at work or at school, and overall deterioration of patients' social and family life. I think it's important to connect the families of patients with local and national arthritis organizations and provide additional resources and support as we often forget about the impact that disease can have on their life.

So in general, early diagnosis and early treatment is the key to better outcomes going forward. We also know that patients who get admitted to the hospital and experience serious complications tend to have longer hospital stay. And the longer the hospital stay, the worse their outcomes are.

So the status of the patient with adult-onset Still's disease who were admitted to the hospital between 2009, 2013, showed that patients on average stayed 7 days in the hospital and patients who died, stayed in the hospital for up to 13 days on average, which led to double the amount of money spent on the hospitalization of this patients who obviously experienced more complex and severe complications. On average, patients who died in the hospital spent $66,000 during their hospital stay.

Dr. Christopher Ritchlin:
So, Olga also to supplement pharmacological interventions. What management strategies do you recommend to your patients to prove their quality of life?

Dr. Olga Petryna:
So I think what's important is in addition to managing this condition with medical treatment is to pay attention to the comorbidities, to their quality of life. For example, patients with severe arthritis that will benefit from proper physical therapy and improving their functional status, educating patients about the signs and symptoms of a life-threatening complications, which would lead to early hospitalization and early treatment can significantly improve their outcomes long term.

Dr. Christopher Ritchlin:
Petros and Olga, thank you for a really great discussion tonight about systemic juvenile inflammatory arthritis and adult-onset Still's disease.

So in conclusion, systemic juvenile inflammatory arthritis and adult-onset Still's disease represent the same disease continuum with different ages of onset. Patients with adult-onset Still's disease experience substantial economic and mental health burden.

A multidisciplinary team is needed to properly care for patients. And of course, greater disease awareness is essential to reduce the time to diagnosis of patients with adult-onset Still's disease. I want to thank the speakers tonight, Petros and Olga, for your thoughtful and well-delivered presentation.

Dr. Christopher Ritchlin: Thank you.

Dr. Olga Petryna: Thank you.

Dr. Petros Efthimiou: Thank you.

Announcer:
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