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Medical Detectives: How to Optimize the Diagnosis of Still's Disease Patients

Announcer:
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This episode of Living Rheum, titled "Medical Detectives: How to Optimize the Diagnosis of Still's Disease Patients" which is sponsored by Novartis US Clinical Development and Medical Affairs. The host and speaker have been compensated for their time. This program is intended for health care professionals.

Here's your host, Dr Jason Liebowitz.

Dr Liebowitz:
In 2018, The Big Sick explored the care of a patient with Still's disease. However, most people have still never heard of this disease. What can be done to increase awareness and improve the diagnosis of Still's disease? This is ReachMD, and I'm Dr Jason Liebowitz.

Joining me to discuss how we can optimize the diagnosis of Still's disease is Dr Bella Mehta. Dr Mehta is an assistant attending physician at the Hospital for Special Surgery and an assistant professor of medicine at the Weill Cornell Medical College in New York City. She specializes in research and care of patients with different rheumatic conditions, including Still's disease. Dr Mehta, thanks for being here today.

Dr Mehta:
Thank you, Dr Liebowitz for this kind introduction, and having me here talking about Still's disease. This is a particularly interesting topic for me, and I see a lot of patients with Still's disease, so looking forward to talk to you more about it.

Dr Liebowitz:
Me as well. To start us off, Dr Mehta, what are some of the key clinical features of Still's disease?

Dr Mehta:
The most common clinical features include quotidian spiking fevers, sore throat, arthritis, and evanescent rash—which is often called a salmon rash—which is on the chest and the back of these patients, elevated liver enzymes, lymphadenopathy, hepatosplenomegaly, and sometimes serositis. Of course, rheumatologists may not see all the features in these patients. For example, the salmon or the evanescent rash is rare, and in the worse groups, may not be looking the same as the typical textbook pictures. Spiking fevers may not occur at the same time in the day. So often patients complain of fevers which are happening over many, many weeks, but whenever they come in the morning to see a rheumatologist or a physician, the fevers are never there because these fevers are usually evening fevers. So again, it's important to recognize that this can happen outside the patient visit. Sometimes the first manifestation that these patients can present can be macrophage activation syndrome, which is a complication for Still's disease. Again, often it can be life-threatening, so important to recognize it early on.

There are 3 different clinical patterns which are more or less identified. Again, this is somewhat theoretical because I've seen patients going from one clinical pattern to the other. Nevertheless, there are the 3 patterns include the monocyclic pattern, which is c haracterized by a single systemic episode, and then the patients don't have it again. A polycyclic pattern, which is characterized by multiple flares lasting for sometimes a year or longer and alternating with remissions, which can last for many years, too. And the much more severe is the chronic pattern, which is recognized by persistent disease activity, has persistent polyarthritis, and doesn't go into remission that easy and is most difficult to treat.

Dr Liebowitz:
Thank you so much for that discussion. Can you tell us about some of the diagnostic criteria that are used for patients with Still's disease?

Dr Mehta:
So, there are several diagnostic criteria that are used for patients with Still's disease. The first one, I think, is the Yamaguchi criteria, and over the years there's Fautrel criteria, Cush criteria, but I think it's important to recognize that the criteria are just a guideline which can be used in cohorts or clinical trials. But clinicians need to be aware of the bigger picture symptoms that we talked about, mainly fevers that are lasting for more than 1 or 2 weeks (and these are pretty high fevers), arthralgias or arthritis, sometimes the rash that we discussed, sometimes leukocytosis, sore throat. And all of these criteria give points to each of these symptoms and adding them up can help you make a diagnosis. But clinically, I think, these are just a guideline. If you have enough of the symptoms and all the other differential diagnoses are ruled out, a Still's disease diagnosis can be made.

Dr Liebowitz:
Thank you so much. And what are the primary issues that may contribute to the diagnostic challenges when facing Still's disease?

Dr Mehta:
There are several issues here. One of the first ones I will say that we just mentioned is sometimes the patients have fevers in the evenings and they are coming to the physicians in the morning, and they are asymptomatic at certain periods of time. The other thing is that different patients can present with different features, and the systemic nature of the disease and the wide diversity of potential symptoms makes it difficult for recognition and even referrals, so sometimes these patients are not referred to rheumatologists for months, or even years, because nobody's thought of it, or thought of referring them to a rheumatologist.

Again, you know, there is a wide differential diagnosis when it comes to a diagnosis of patients with Still's disease. It could be infections, malignancies, and other rheumatic diseases. And again, even in the patient who's already diagnosed with Still's disease, when they start having flares sometimes, we don't know if it's either because of an infection which is causing fever or a flare causing fever, because some of the medications we give these patients also tend to immunosuppress and make them much more prone to infection. So, these are like diagnostic challenges sometimes for these patients. And again, sometimes when the patients are in remission, you don't even have autoantibodies or something to rely on to diagnose these patients.

I think sometimes, the other problem is that the patients just have 1 major manifestation—for example, a rash—and they keep going to a dermatologist and may not even have mentioned about other symptoms that they're getting, such as arthritis. So again, I think other subspecialty physicians around rheumatologists also need to be aware and appropriately refer these patients. Also, a lot of rheumatologists are not very familiar with it because we don't see this as often. It's a rare disease and having it at the back of the mind is important to be able to recognize and treat these patients. Often, some of these patients are referred to, tertiary care centers because rheumatologists in tertiary care centers sometimes are more familiar with it and more comfortable treating this.

Dr Liebowitz:
Thank you, those are very helpful insights. And Dr Mehta, which biomarkers currently exist to aid in the diagnosis of Still's disease, and which biomarkers are under research with respect to this condition?

Dr Mehta:
I think clinically, the biomarkers that we send out most commonly are serum ferritin, C-reactive protein and ESR. Some of the other routine biomarkers include glycosylated ferritin, which is not available widely, but still, in some cases we can. The other one is serum amyloid A and calprotectin. I think between these and the clinical features, it is easy to recognize Still's disease if you're looking for it in a particular patient.

Some of the other potential biomarkers for research, which are used either in some clinical trials or cohort settings are serum cytokine levels, which is, IL-1, IL-6, and IL-18. These can also be sent out as a part of a cytokine panel which is available in a lot of labs. However, chemokines, such as CXC-chemokine ligands 10 and 13 are much more research lab-based and cannot be sent out. Still, recognized as important in Still's disease. Advanced glycation end products, or AGES, and soluble receptor for AGES are also some of the other potential biomarkers for research. I think in the future, we'll be using these much more, but currently, it's difficult to send out and we're not 100% sure of its clinical utility, either in recognizing the disease or its flares. But clinically, ferritin does rise during flares, in most cases. So does, CRP. So, patients with the disease often get these biomarkers done, at least the common ones, on a regular basis.

Dr Liebowitz:
And looking to the future, what obstacles may prevent rheumatologists from reaching an accurate and timely diagnosis of Still's

disease?

Dr Mehta:
I think there's a need for more specific biomarkers, and seeing how they're exactly clinically relevant, and other indicators of disease, and understanding when to use them is going to be the key in the future. Also, I think, overall, a lot of health care providers who are seeing these patients, such as dermatologists for example, need to recognize Still's disease and refer these patients early on so that there's a timely diagnosis. There is data saying that if the patients are treated early, there is less damage and less long-term consequences for these patients. So, in order to do that, we need to also have our referring providers know enough about Still's disease. Also, better integration of the medical record systems to identify patterns that may not be apparent to individual clinicians will be helpful. Especially between the different subspecialties.

Dr Liebowitz:
Wonderful. And with those forward-looking thoughts in mind, I want to thank my guest for helping us better understand the diagnosis of Still's disease. Dr Mehta, it was a great pleasure speaking with you today.

Dr Mehta:
Thank you so much for inviting me, and I think it's important to take the key takeaways here, is that Still's disease is a rare disease, but can be recognized clinically with fevers, lymphadenopathy, arthralgias, arthritis, sometimes serositis, and it is important to refer these patients early. Rashes may not be easily seen in all patients, and so relying on the typical evanescent salmon rash may not be the only thing. Looking at all of the clinical features together are important. Also looking for complications such as macrophage activation syndrome will improve mortality and morbidity in these patients.

Announcer:
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