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Evaluating Eosinophilic Disorders: A Dive into Diagnosing EGPA & HES

Announcer:
You're listening to ReachMD, and this is *Deep Breaths: Updates from CHEST*. This episode is brought to you by the American College of CHEST Physicians in collaboration with and paid for by GSK.

Your host today is Dr. Jared Silver, allergist immunologist, and a US medical lead for GSK.

Dr. Silver:
This is ReachMD. I'm Dr. Jared Silver and today I'm delighted to be joined by Dr. Praveen Akuthota, Pulmonologist from U.C. San Diego Medical Center in California to discuss diagnosing two diseases associated with elevated eosinophils: eosinophilic granulomatosis with polyangiitis or EGPA for short, and hypereosinophilic syndrome, also known as HES. Dr. Akuthota, welcome.

Dr. Akuthota:
Thank you so much, Jared for having me. I'm looking forward to the discussion.

Dr. Silver:
Wonderful. Let's begin by taking a look at the diagnostic landscape for these two diseases, Praveen. Can you please give us an introduction to what HES and EGPA are?

Dr. Akuthota:
I'll start by what these two things have in common. HES, or hypereosinophilic syndrome or actually more appropriately hypereosinophilic syndromes and EGPA or eosinophilic granulomatosis with polyangiitis are both diseases with very high eosinophil counts and multi-organ involvement. So, that's the major overlap between the two and that's and then how to differentiate them and the details of each one are a little bit unique to each.

So, HES is a heterogeneous group of diseases. There's different pathways that can lead you to HES, whether it be a myeloproliferative or a bone marrow-derived disease entity whether this be more of a lymphocytic or a lymphocyte driven hypereosinophilia or an idiopathic form of HES. So, really a heterogenous group of diseases that are tied together by hypereosinophilia, and we generally define hypereosinophilia as 1,500 account absolute eosinophil count of 1,500 cells per microliter on two separate occasions, usually thirty, spaced thirty days apart and that's one of the standard definitions of hypereosinophilia in the literature. And then in association with those high eosinophil counts are various end-organ manifestations. Whether they be sometimes lung involvement, sometimes often skin involvement, cardiac involvement, neurological involvement. So that's how I would in general encompass HES. And that's opposed to EGPA, which is also a disease with high eosinophil counts and I specifically don't say 'hypereosinophilia' just because the diagnostic criteria is a little different, and often in most diagnostic schema include an eosinophil count of 1,000 or greater, which is a high eosinophil level, but not technically hypereosinophilia. But EGPA, again, has a high eosinophil count but is really rooted in with a couple of different anchor points. And that includes a history, often or almost always of asthma, often a history of other atopy particularly upper airway chronic rhinosinusitis, and then can also involve other organs, and often will have vasculitic manifestations, as well. So, EGPA's an entity that lies at the intersection of atopy in asthma with small vessel ANCA-positive vasculitis. So, that's the core of EGPA.

Dr. Silver:
I think that's a great foundation upon which to carry on our discussion about diagnosis and management and the various challenges distinguishing between these disease entities. And that leads me nicely to my next question for you. So, what makes these two diseases so challenging to diagnose and tell apart from one another? Can you dive in and tell us a little bit about that?

Dr. Akuthota:
Yeah, it is difficult, Jared, just because the commonalities of having hypereosinophilia, there's not a lot of things out there that cause very high eosinophil counts in the thousands, and then sometimes in hypereosinophilic syndromes tens of thousands. So, these are two of the major things you would think of with the high eosinophil level when other external causes are eliminated or at least worked up, and then the other challenging point is a lot of the clinical manifestations really do overlap. Both can have respiratory manifestations. So, while EGPA often has an asthma prodrome or a history of asthma, HES also can have respiratory involvement and it may not be specifically airway involvement, but it can be dyspnea from eosinophilic infiltration in the lungs. So, you can imagine that a lot of the clinical presentation can overlap. So, that's really why it is so challenging.

Dr. Silver:
Alright, terrific points, particularly as it relates to the overlapping features, overlap syndrome, the marked elevations of EOS, certainly the rarity of disease and that it can take time to evolve and present itself in a way to declare itself enough for detection I imagine also are challenges, are they not?

Dr. Akuthota:
Yeah, indeed. I think there's a lot of steps that have to happen. You have to have presented first to medical care, you have to have had labs that will detect the high eosinophil count, and then you'll have to have somebody who will notice that there's a high eosinophil count. The absolute eosinophilia is sometimes buried, and we all know this, we get CBCs every day on tons of people and we're often looking for the top line items on the CBC and sometimes the differential and some of the other parameters on the CBC are buried and escape clinicians' attention. So, people are just not tuned into these diseases into hypereosinophilia in general and sometimes just even getting to workup is challenging. And beside the rareness, there's a few other things. There's the tempo: people present at different tempos. They tend to accumulate disease manifestations over time, so people are thinking of the specific boxes of the particular manifestations. Somebody might have GI involvement from either EGPA or HES and present to a gastroenterologist and hypereosinophilic conditions may not be on the radar screen or somebody might present to a dermatologist for those manifestations and those things might build up over time. But there's a few things we can, not to be too nihilistic about it, there's waving flags to tell us that this might be EGPA, or this might be HES.

And then again, the sinus disease and then with EGPA, there's things that seem vasculitic, like renal disease in particular, neurological symptoms in particular mononeuritis multiplex, which is something that's often seen in EGPA. Those are things that will key you into EGPA. Those are less HES-like. And that's opposed to HES, which has a few other things that are more common: cardiac involvement is more common HES, dermatologic manifestations, particularly in lymphocytic hypereosinophilic syndrome or LHES can be quite common as well. Neurologic symptoms, as well, are something to key into for HES.

Dr. Silver:
Praveen, terrific review of the diagnostic challenges and the foundational elements necessary to understand HES and EGPA. Now that we have a sense of those challenges, can you walk us through a patient, perhaps one that you have worked up in your own practice, to help us understand the diagnostic steps and challenges?

Dr. Akuthota:
Yeah, absolutely. Let me let me tell you about a patient I prepared for discussion today. A 45-year-old man who I saw who's a non-smoker, a previous diagnosis of asthma from childhood, but not so much in his twenties and thirties after he became a young adult. And he presented to me with progressive dyspnea, fever, peripheral neuropathy, constitutional symptoms, and he had a productive cough with bloody sputum, and he also had some upper airway congestion, as well. He told me that his asthma had been worsening in recent years, over the last three, four years and now it was refractory to standard asthma therapy, so high dose inhaled corticosteroid, long-acting beta agonist, and also refractory now to being on chronic OCS, 10 mg daily of OCS. So, the first thing with him that I was able to do was look back through his chart and recognize that prior to being on oral corticosteroids, he had regularly had high eosinophil counts. So, he had eosinophil counts in the 1,000s often on checking CBC. So, thinking about him syndromically, he was already starting to meet some of the criteria for EGPA using an older American College of Rheumatology classification. He met four of six of asthma, eosinophilia, peripheral neuropathy, mononeuropathy or polyneuropathy, he had more of a polyneuropathy, he had infiltrates on chest imaging. So, I got a chest CT, which showed ground glass opacities. And he also had sinus disease so those five of the six criteria. The sixth criteria is biopsy, which he actually eventually ended up getting because of the bloody sputum and some other considerations and that also showed cinched the diagnosis and showed perivascular eosinophilic infiltrate; not frank vasculitis, but really the perivascular infiltrate is enough to make the pathologic diagnosis as well. So, that really keyed me in on him to a diagnosis of EGPA. But in some patients, I'm also thinking is this EGPA or HES and I might do other workup, as well, that's keyed in more to HES like a bone marrow biopsy peripheral flow for lymphocyte clones tryptase level vitamin B12 level cytogenetics, so those are all things I would do potentially to try to cover the HES end of the spectrum, as well. I did other standard things like PFTs as well, which showed a severe obstructive

pattern, and then re-checked his eosinophil count, which was actually high, despite steroids. It was 3,170, despite steroids. He had a high IgE level of 2,220 and that is something that I'll often see in EGPA, as well. He had a normal tryptase, which goes away from HES and also critically and I'll end with this, he was ANCA-negative. So, I often hear that if somebody's ANCA-negative they, they can't have EGPA and that's not the case. Actually, in case series, two-thirds of patients are ANCA-negative with, with EGPA. So, you can have a positive ANCA, but you don't have to have a positive ANCA in EGPA. So, that was the case that I saw that I wanted to highlight to the listeners about a diagnosis in this realm.

Dr. Silver:
For those just joining us, this is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Jared Silver and I'm speaking with Dr. Praveen Akuthota about the challenges of diagnosing patients with eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndromes.

Praveen, let's turn our attention now to management of HES and EGPA. Both of these disease entities require a multi-disciplinary approach, so can you tell us which specialists are involved in that process in your experience, and when you recommend involving other members of the care team?

Dr. Akuthota:
Yeah, thanks Jared. There's a lot of people who end up getting involved in, in HES and EGPA from the primary care physician, who might be the initial point of contact and then a lot of who they might present to is dictated by which symptoms they might manifest with. So, from the EGPA side, often rheumatologists might get involved because of vasculitic manifestations, so that's a big dichotomy; pulmonologists, allergists, for respiratory symptoms versus rheumatologists for more of vasculitic symptoms. But then there's disease-specific people for both entities: gastroenterologists, cardiologist, neurologists, etc. So, it really does take a village and sometimes this glut of specialists that end up getting involved is great in some ways but because everyone's looking at their little thing, there's often a delay in diagnosis from disease onset so that's actually been found to be up to four years in the literature. So really, there can be quite the delay in diagnosis. But after the diagnosis is made, really that multi-disciplinary care and approach in communication is really essential. And I should also add it's important to bring the patient in, as well. Shared decision-making for the complexities of management for entities like EGPA and HES is really critical.

Dr. Silver:
Now, before we close, Praveen, do you have any other final thoughts you'd like to share with our audience, perhaps capturing some of the most salient points of today's conversation?

Dr. Akuthota:
Yeah, thanks for the opportunity to do that. I think there's a few things I would highlight to close: that first, even though these are rare diseases, they are important to recognize because, particularly in a pulmonary practice you will see patients with high eosinophil counts, and it's important to understand what the potential diagnoses underlying high eosinophil counts are and allow you to workup eosinophilia. Many people will see relatively few cases. But if the case is recognized, if the disease is recognized, you can have a major impact on patient's quality of life because then treatment can be dictated by the diagnosis. And you can also avoid on both the vasculitis EGPA side and the hypereosinophilic syndrome side and organ manifestations that are irreversible: neurologic changes, kidney, kidney damage, etc., toxicities from oral corticosteroids, which are a big thing. So, that patient that I had told you all about could've had many problems from chronic oral corticosteroid use over decades if his disease was not recognized. So, it's really crucial to find an efficient pathway to diagnosis.

The second thing that I would point out really dovetails from that, that delays in diagnosis allows for disease progression. And that can, end up having cumulative, multiplicative impacts on patients' quality of life. I would also emphasize, again, the importance of a multi-disciplinary approach: Bring in your team of specialists once the diagnosis is made; it's cliché but it takes a village. And then communication between that multi-disciplinary team is really critical and can help with management and optimize long-term outcomes.

Dr. Silver:
Well, with those final thoughts in mind, I want to thank you Praveen, for providing your insights on HES and EGPA today. Delighted to be here with you for this conversation. Thank you for joining us.

Dr. Akuthota:
Absolutely. This was fun.

Announcer:
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