Dr. Jason Barnes:

Hey there. Welcome to another episode of, ENT in a Nutshell. My name is Jason Barnes and I'm again, joined by Dr. Matt Koster and Dr. Garret Choby. And today we'll be discussing EGPA, or Eosinophilic Granulomatosis with Polyangiitis. Dr. Choby, Dr. Koster, thanks again for being here.

Dr. Matthew Koster:

Thanks for having us.

Dr. Garret Choby:

Thank you.

Dr. Jason Barnes:

Dr. Koster, from the rheumatology side, could you start with just telling us how a patient with EGPA, which is also known as Churg-Strauss disease, how they often present?

Dr. Matthew Koster:

Certainly. So to contrast it somewhat with patients who ended up presenting with GPA, or what was formerly known as Wegener's, these patients can also have Sinonasal dysfunction with chronic rhinosinusitis. They'll often have more nasal polyps, and Dr. Choby can perhaps speak a little bit more to that, but this is often in the context of patients who have had long standing asthma, or in adults having adult onset asthma. Now, when you think of the evolution of EGPA, there's a concept of having different phases. So there's what we call a prodromal phase, meaning patients who may have more nasal polyposis asthma, and then may start developing some symptoms that are kind of constitutional in nature, weight loss, fever, malaise, myalgia, arthralgia, et cetera. Then there seems what we call an eosinophilic phase in which they have those symptoms that I just mentioned, but then they start having a rise, or a further increase in their peripheral eosinophils.

Dr. Matthew Koster:

And often those levels that you're going to see are higher than 10% of your white blood cells are going to be eosinophils, or greater than an absolute value of 1,500. When the eosinophils start increasing, they're going to start depositing in different organs. So it can be in the sinuses, that can cause a localized inflammation and nasal polyps, but it can also be in other areas like the lung, causing more refractory asthma or eosinophilic asthma, or some findings of pneumonia, that if you do a bronchoalveolar lavage, you'll see high levels of eosinophils present in the lavage material, consistent with eosinophilic pneumonia. But they can also end up having it deposit in the heart causing myocarditis or the GI tract causing diarrhea or abdominal pain. And so it's that infiltration of the eosinophils that can cause multiple different organs to be effected. And then there's a third or kind of final phase that sometimes can be in tandem with a significant increase in eosinophils, but this is the vasculitic phase.

Dr. Matthew Koster:

So this is where you're going to start seeing things like skin nodules, that if you biopsy them, you're going to end up seeing findings of eosinophilic infiltration, and findings of leukocytoclastic vasculitis. That can also be seen that classical palpable purpura that's talked about. And then also findings of alveolar hemorrhage. So bleeding in the lungs and respiratory dysfunction, mononeuritis multiplex, which is again, things like wrist drop, foot drop, they less commonly have glomerulonephritis. So renal

dysfunction compared to patients with GPA, this is probably to the tune of 10% to 20%, but can be present and significant. So that's the range of the different phases. And so you can catch them at different time points, but it's hard to solidify a diagnosis if they're in that very early prodromal phase.

Dr. Jason Barnes:

Sure. And Dr. Choby, when you see these patients in clinic, what's their typical presentation and how do you evaluate them to start?

Dr. Garret Choby:

So this is a disease that's not always very apparent at the outset of their ENT evaluation. And I will also describe it to a certain extent in contrast to GPA. And what I would say is that this disease, as far as a rhinology ENT manifestation is more along the lines of chronic sinusitis, often with nasal polyposis, asthma, usually adult onset, and then eosinophilia. And that's in contrast to GPA, which is another vasculitic disease, but more typically presents with ongoing nasal crusting, septal perforations, saddle nose deformity, and ischemia in the nose. So we do see a lot of nasal involvement. And again, that's more chronic rhinosinusitis, which tends to be with nasal polyposis. There can also be ear manifestations. So classically that's going to be a serous otitis media, and there may be sensorineural hearing loss associated with it as well. And many patients have symptoms of allergic rhinitis and nasal obstruction.

Dr. Jason Barnes:

Dr. Koster, can you describe a little bit the pathophysiology of the disease? What is it, and what causes it?

Dr. Matthew Koster:

Sure. So this has again, kind of two somewhat distinct, but overlapping underlying etiopathogenic problems. So they're, again, similar to GPA, has an underlying genetic predisposition of different polymorphisms that can increase someone's likelihood of developing this condition, but often requires an additional stimulus. That stimulus can end up being environmental exposure, infection, drug, inhaled antigens, et cetera. There's the ANCA mediated inflammation that was described in the podcast focusing on GPA, in which the neutrophils play a predominant role in getting primed, and then kind of increasing the proinflammatory mediators that cause this cyclic pathway of neutrophil priming and inflammation. There's the contrary eosinophilic portion of the etiology in which Interleukin 5 is extremely important in this sector of the pathogenesis. Interleukin 5, or IL5 ends up having an increase in eosinophil per generators. And so they mature and then they'll end up invading into the bloodstream, and then will in high level start invading into the tissue.

Dr. Matthew Koster:

Now eosinophils are not really white blood cells that we need, to be perfectly honest. Often they're used for fighting off parasitic infections. It's not something in which you need these in a fighting off an infection standpoint. And so it's often more in an allergic stance. And so not to get too into the weeds, but when you're talking about lymphocytes, there's a TH1 pathway, which is predominantly your T cells that are like lymphocytes. For a TH2 pathway, it's more of an allergic reaction. And that's where the eosinophils are present, which is why urticaria often has eosinophils involved. It's that upregulation of IL5, and the kind of cyclical increase in eosinophils that leads to that perpetual elevation of eosinophils.

And in some cases dramatic rises that leads to eosinophilic deposition and tissue that can lead to local inflammation and organ damage.

Dr. Matthew Koster:

So there's kind of the vasculitic stance, and the eosinophil stance that can overlap, and both can have issues in the lungs, but it's more the eosinophil infiltration that's more for the sinuses, the GI track, the cardiac structures. Whereas the ANCA mediated inflammation is going to be more like the kidneys, to some extent the lungs, and the nerves. And so it's trying to understand both those mechanisms, which we'll end up going a little bit more further into detail about why there's different medications that work a little bit more effectively in this condition as opposed to GPA.

Dr. Jason Barnes:

And I'm sure on the rheumatology side, there are a number of things on your differential diagnosis, but Dr. Choby, from an ENT standpoint, when you evaluate someone who ends up being diagnosed with EGPA, what else is on your differential diagnosis?

Dr. Garret Choby:

So with this disease process, again, because we're typically seeing things like CRS with nasal polyps, asthma and eosinophilia, we think of other diseases that may manifest itself similarly. So we think of things like AERD, would be a very classic one to think about. That disease we've talked about in another podcast, but nasal polyposis, usually elevated eosinophil level, asthma, and then a reactivity to aspirin products will be one we think about a lot. It could be routine CRS with nasal polyposis, as well as asthma, which do commonly occur together with or without the aspirin sensitivity. Allergic fungal sinusitis could be entertained in a differential as well, commonly an eosinophil manifested disease. Then other things as well, more unusual, but hypereosinophilic syndrome would be one, or allergic bronchopulmonary aspergillosis is something that could be entertained as well.

Dr. Jason Barnes:

And Dr. Koster, when you see these patients, what's your workup for them?

Dr. Matthew Koster:

So similar to any patient that we're evaluating for multisystem disease in the spectrum of ANCA associated vasculitis, it's going to be a very thorough history and physical exam to evaluate the different organ systems that may have any pathology or abnormalities to further investigate with either biopsy or imaging studies. Most of these patients will often have already had CBCs that have been evaluated showing evidence of eosinophilia. We will look at these and trend these over time to see has been persistently or periodically elevated. Things in which they have persistent elevation greater than 10% of their peripheral eosinophils is an important finding in these patients, and often pathognomonic, to some extent. They'll typically have asthma. And so whether they're not quite diagnosed with that, we will often send them for pulmonary function testing with a methycolene challenge to identify that. In addition, nitric oxide testing, either nasal or oral, can show elevated levels of exhaled nitric oxide. Which is a finding seen within patients with asthma.

Dr. Matthew Koster:

Evaluating different organ systems again. So looking at the lungs with a chest x-ray or a high resolution CT scan to look for abnormalities, CT scan of the sinuses if felt necessary by our ENT colleagues,

evaluation for renal dysfunction, a full neurologic examination to make sure that there's no deficits. And then in patients with significant inflammation, so high inflammatory markers like sedimentation rate or C reactor protein, and if they look I'll, or if they have findings suggestive of heart failure, those patients will often end up getting an echocardiogram, and/or a cardiac MRI to look for any concern of myocarditis, which is a very poor prognostic finding in these patients and requires aggressive treatment.

Dr. Matthew Koster:

Patients who have chronic diarrhea or abdominal pain may require a CT scan of the abdomen. And so often it's trying to evaluate these different organ territories, evaluate them by exam, laboratory and also imaging. We do check ANCA serologies for these patients, but they're not as helpful in comparison to patients with GPA. For the frequency of finding ANCA serologies in these patients, it's typically around the frequency of 40% to 60% of patients may be ANCA positive. If they are, they're more commonly p-ANCA myeloperoxidase antibody positive, but it's truly a flip of the coin sometimes as far as whether they will be or not. So negative ANCA serologies with a correct constellation of symptoms and persistent eosinophilia still has a strong suspicion for this disease. So checking those labs alone, and seeing them negative is not sufficient to rule out this condition.

Dr. Jason Barnes:

And is there a diagnostic criteria to formally diagnosis this?

Dr. Matthew Koster:

There's not actually a diagnostic criteria that we end up using for this. However, there is classification criteria that we end up using, it's rather old. The last time that this was done was in 1990, and that was the American College Rheumatology classification criteria that was used at that time. Those are in the works of being updated through an international collaboration that is trying to update these things now that we have ANCA serologies, because actually the ANCA testing was not even included in the initial classification criteria from 1990. The classification criteria from that time and these while used for research purposes and not for diagnosis are helpful to remind you what are areas to consider, but the six different things to consider for possibility are asthma: eosinophils greater than 10% of your leukocytes, mononeuropathy or polyneuropathy, so mononeuritis multiplex, migratory or transient pulmonary opacities, paranasal sinus abnormalities, or a biopsy of a blood vessel showing accumulation of eosinophils and extra vascular area. So if you have four or more of those, that would be what fits classification criteria. But again, not to be used for diagnostic purposes.

Dr. Jason Barnes:

And just to kind of push into that a little more, how do you diagnose someone with EGPA?

Dr. Matthew Koster:

So similar to GPA, or Wegener's, it's really a clinical diagnosis. And so you have to evaluate the patient and understand the clinical symptoms. Labs, imaging, biopsy can all be helpful. Biopsy, if positive, can be considered confirmatory, but you have to understand that there are other things that can end up causing similar findings: systemic infections with parasitic infections, hypereosinophilic syndrome, whether that's primary or secondary as mentioned by Dr. Choby. And in addition, there's a higher frequency of patients who have, for instance, eosinophilic asthma. So that has a frequency of one in 13 people in the US. I'm sorry, asthma itself is one in 13 in the US. Eosinophilic asthma is about one in 250.

Dr. Matthew Koster:

Eosinophilic pneumonia about one in 100,000, but EGPA, the annual incidence of that is about one to two per million. So you've got to think of these more common things first, if the clinical situation is not likely, but certainly a patient with the right constellation of symptoms, persistent eosinophilia, constitutional symptoms, elevated inflammatory markers, sinus abnormalities. If they have a biopsy that's positive, that's conclusive, those would be the ones that for sure have the diagnosis, the other ones, you have to try to bring enough information to raise your suspicion to initiate treatment.

Dr. Jason Barnes:

And what is the treatment?

Dr. Matthew Koster:

So there's a similar to our other diseases, but specifically in vasculitis, you have to understand how severe the disease is to understand and guide how aggressive to be with treatment. There is something called a Five Factor Score that had been identified through the French Vasculitis Study Group that looks at the different involvement and severity of the organ manifestations in the heart, lung, GI and central nervous system. And if they have one or more of those involvements, that is considered severe disease and requires typically induction with something like cyclophosphamide and high dose steroids. For patients who have what we call lower risk disease, or Five Factor Score of zero, which are often patients who may have some mild lung involvement or sinus nasal abnormalities, but don't have severe organ dysfunction. Those patients may be treated in some circumstances with a course of moderate dose of prednisone with taper and may have improvement and uncommon remission, but may at least have significant symptom resolution and may not require ongoing immunosuppressive therapy.

Dr. Matthew Koster:

Most patients will however have return of asthma and sinus symptoms, which are common to recur, and will respond to steroids. But when you taper them have relapses or flares and will often require disease modifying agents such as methotrexate or less commonly prescribed things like Azathioprine or Mycophenolate. There is a new medicine that has been recently approved within the last 12 to 18 months for the treatment of EGPA. It's a biologic medicine called Mepolizumab, or its trade name is Nucala. It's a inhibitor of Interleukin 5, which I explained was a very key integral role of the eosinophil deposition. When you're having patients who have predominantly asthma or sinus disease, we find that Mepolizumab is very helpful. However, patients who have vasculitic involvement, so kidney alveolar hemorrhage, and the long mononeuritis multiplex, those are patients who may not respond effectively to Mepolizumab, and may require things like Cyclophosphamide, or the medicine that's approved for GPA, but not EDPA, which is Rituximab. And that's currently being trialed in several different countries for the use of EGPA, but with variable effect.

Dr. Jason Barnes:

And Dr. Choby, what is your treatment approach for patients with EGPA who present to your clinic specifically with sinus symptoms?

Dr. Garret Choby:

So this disease is primarily managed and approached much like other issues of chronic rhinosinusitis. I mentioned earlier that these patients oftentimes will have nasal polyposis and directed treatment in regards to topical steroids. And even systemic steroids may be indicated. I will mention, we just

published a study last month, looking at EGPA manifestations in the sinuses. And that was really spearheaded by Dr. Lowe and Dr. O'Brien. In our study, which was, I believe the largest EGP series to date published are looking at sinus issues, only 50% of those patients actually had nasal polyposis. So perhaps in some larger series such as that, less polyposis than we originally imagined. We also set to look at things like, could we predict what factors of their disease may make their sinus disease worse? And we couldn't really pick out any specific factors. We looked at their ANCA positivity, the level of their eosinophilia, et cetera.

Dr. Garret Choby:

And none of those things really were shown to have worsened outcomes in regards to symptom management or worsened Lundbeck high scores. So we ended up treating these patients like a routine sinusitis patients, we'll treat them medically as appropriate with our typical systemic and topical medication regimens. And then we will also occasionally operate on these patients from a sinus standpoint. Although we think that they probably do less well overall postoperatively, then more routine cases of nasal polyposis or CRS. I also mention their ears are oftentimes involved. And that's typically things like Otitus media or sensorineural hearing loss. And they may also benefit from addressing that with things like myringotomy tube placement or topical drops for the ears as well.

Dr. Jason Barnes:

Sure. And Dr. Koster, how do you counsel patients on followup prognosis outcomes and expectations?

Dr. Matthew Koster:

So the prognosis of this condition really depends on how severe the manifestations are, and how quickly and appropriately treatments are enacted. For patients who have severe lung disease or kidney disease, damage may occur prior to initiation of treatments. And therefore they may have ongoing dysfunction with respiratory compromise or renal dysfunction. That may in some circumstances require renal replacement therapy like dialysis, but for patients who don't have severe disease at the beginning that has led to damage, often they will have a pretty significant recovery with improvement of their cardiac GI and renal manifestation. So the cardiac involvement with myocarditis can be a poor prognostic factor. The thing that patients with EGPA need to understand though, is that while we can very effectively treat the vasculitic manifestations with treatments, the features of asthma and often nasal crusting and chronic rhinosinusitis may be difficult to get those patients into full remission without any recurrence.

Dr. Matthew Koster:

So those are the most frequently relapsing symptoms. And so while treatment with immunosuppressive medicines can be very effective for the treatment of the vasculitic manifestations, we often have to rely on ongoing assistance and guidance from our ENT and pulmonary colleagues to make sure that they're optimized with their sinus rinses and other sinus targeted treatments, as well as inhaled corticosteroids and asthma-related medications. The treatment with things like Mepolizumab has been quite helpful in reducing those chronic recurrent relapsing features of the sinus and asthma. And that's bringing us into a new era of better control, but of the three different subtypes of ANCA vasculitis, the one that has the most frequent relapses, again with sinus and asthma, is EGPA.

Dr. Jason Barnes:

Well, this has been a super helpful discussion for a disease process that we don't often see. Before I go into the summary, Dr. Koster, Dr. Choby, anything you would add?

Dr. Garret Choby:

No, I think I was very thorough. I appreciate the nice summary and guidance by Dr. Koster.

Dr. Matthew Koster:

Yeah. The only thing that I would add is that there are evolving clinical trials that are being focused on for EGPA. So there will be ideally new medications that will be available that we're not even talking about right now, sometime perhaps in the next two to four years, which is just showing kind of the evolution and the importance of these diseases that are being recognized more commonly now.

Dr. Jason Barnes:

Awesome. Well, thank you so much. I'll move into our summary here now. EGPA or eosinophilic granulomatosis with polyangiitis is a small vessel vasculitis. And in contrast to GPA, this more often presents with asthma as the cardinal feature, though ENT symptoms can include serous otitus media and sensory neural hearing loss, allergic rhinitis, nasal obstruction, and CRS with nasal polyposis. Workup includes lab work with ANCA, but only 40 to 60% of these patients will show ANCA positivity. But in these cases, p-ANCA is more common in contrast to GPA, which is more common to have c-ANCA. Classification criteria are used to describe the features of EGPA. And this includes greater than 10% eosinophillia, Mononeuropathy or Polyneuropathy, migratory, or transient pulmonary opacities, paranasal sinus abnormalities, and a biopsy of blood vessels showing accumulation of eosinophils. Treatment varies, but can include steroids and other medications such as Cyclophosphamide, Methotrexate, Azathioprine, and Mycophenolate. And Dr. Koster mentioned Mepolizumab, the IL5-specific treatment.

Dr. Jason Barnes:

And from the ENT side of things, we treat them like a CRS patient, possibly providing sinus surgery, though it might not be quite as successful in these patients. Dr. Koster, Dr. Choby, anything else you'd like to add?

Dr. Matthew Koster:

I think that sums it up.

Dr. Garret Choby:

Yeah. Thanks, Jason.

Dr. Jason Barnes:

Yeah. Thank you all so much. Really appreciate it. We'll now move into a question asking portion of this episode. As a reminder, I'll ask a question, wait a few seconds, and then provide the answer. So the first question is, what is the most common presenting feature of EGPA? The most common presenting feature of EGPA is asthma. Next question. Describe the ANCA positivity in patients with EGPA. In EGPA, only about half of patients are going to be ANCA positive. Those who are positive are more likely to be p-ANCA positive. And our final question, what role does sinus surgery play in EGPA? EGPA is a disease that's a little bit more difficult to treat with sinus surgery. It is offered, but we try to limit it, because it might not be as effective as patients with CRS. Thanks so much for listening, and we'll see you next time.