Dr. Jason Barnes:

Hey there. Welcome to another episode of ENT in a Nutshell. My name's Jason Barnes and today we are joined by two special guests, Dr. Matt Koster, a rheumatologist and Dr. Garret Choby, a rhinologist, and we will be discussing GPA. Dr. Koster, Dr. Choby, Thanks so much for being here.

Dr. Garret Choby:

Thanks for having us, Jason.

Dr. Matthew Koster:

Yeah. Happy to be part of this.

Dr. Jason Barnes:

So when we talk about GPA, Dr. Koster, can you tell us what a classic presentation is for someone who has GPA?

Dr. Matthew Koster:

Yeah, certainly. So when we're talking about GPA, just to highlight this condition, it's rare. And I think that's of most importance to explain is that when we're talking about a condition that has an annual incidence of 10 to 20 million per population, many people may not see this disease ever in their lifetime, either internal medicine, surgery, or even some rheumatologists. And so understanding the typical and atypical presentations of this condition is important. From a rheumatologist standpoint, some classic features to consider are patients who have recurrent sinusitis. And so these are patients who end up having ongoing, episodic requirements in which they're treated with antibiotics or steroids, and it can happen for many years. But they'll often end up having additional symptoms beyond that. And so fever, malaise, fatigue. They can also end up having some joint inflammation. Also findings of cough or shortness of breath, specifically, if they end up having some coughing of blood at any point in time, that's very alarming.

Dr. Matthew Koster:

And then other findings that they may not end up disclosing, but things that you can find out through investigations such as renal dysfunction. And also some key features or anyone who has what we call mononeuritis multiplex, so nerve involvement in different territories that are not explained by a single nerve irritation, such as wrist drop or foot drop. So anyone with those constellation of features of multiorgan system involvement should raise the question of a systemic inflammatory disease. And if they're involving the upper airways and the lungs, GPA should be on a high list of differential.

Dr. Jason Barnes:

Sure. And Dr. Choby, when you evaluate patients with GPA in your clinic, what do you typically look for and what do you see? And I think we may have gotten ahead of ourselves too. Can you tell us what GPA stands for and if it has any other names?

Dr. Garret Choby:

Sure. So GPA is the current in vogue name for this disease process, and that's granulomatosis with polyangiitis. This formerly has the name of Wegener's disease, but as with many eponyms that has sort

of gone by the wayside and now more commonly referred to as GPA. When these patients present to our clinic, the most common auto-laryngology manifestation is typically in the nose.

Dr. Garret Choby:

And because this is a condition of vasculitis with granulomatous inflammation of blood vessels in the nose, this results in ischemic changes. The most typical findings that we see are things like septal perforations, and when severe enough it can cause a saddle nose deformity. Many patients have ongoing crusting in their nose from the ischemic changes. And then we oftentimes also see almost an auto-destructive picture. So the inferior turbinates, the nasal floor, the middle turbinates and the lateral nasal wall can progressively become destroyed from this disease process from ongoing ischemia and vasculitic changes. The second thing I'll mention is that this also can affect other areas are related to the otolaryngologist, things like otitis media and hearing loss can occur as well as one of the more classic findings of subglottic stenosis or inflammation in these patients.

Dr. Jason Barnes:

And when you evaluate these patients, Dr. Choby, what else is on your differential diagnosis?

Dr. Garret Choby:

So when these patients come to us and don't have a formal diagnosis of GPA yet, a number of other possibilities can be entertained, especially from a nasal standpoint. We think of things like acute or chronic invasive fungal sinusitis, especially with nasal destructive lesions. Other things like illicit drug use, like cocaine can also manifest itself in this area. We think a little bit about a midline destructive lesion or an NK/T-cell lymphoma, and then other rheumatologic diseases can also manifest similarly, such as EGPA, or Churg-Strauss disease, policondritis or sarcoidosis as well.

Dr. Jason Barnes:

And Dr. Koster, can you tell us what is GPA? Can you tell us a little bit about the pathophysiology?

Dr. Matthew Koster:

Yeah, certainly. So it's not fully understood as far as the exact etiologic cause of this. There's been an understanding that there is somewhat of a genetic predisposition and when there's been a genome wide associated studies that have been done in patients with GPA and also the other subsets of ANCA associated vasculitis, such as EGPA that Dr. Choby mentioned, and then also the third of the three microscopic polyangiitis that doesn't infect the upper airways. There is clustering of certain polymorphisms that are seen that seem to increase the frequency and presence of anti-neutrophil cytoplasmic antibodies, as well as other factors, such as neutrophil dysregulation. So we know that there's some genetic elements, but it's not a directly genetic disease. And that's something that patients always ask. But it's something in which if you have a first degree relative, you probably have a 10 to 100% increased risk or 10 to 100 time I should say, increased risk.

Dr. Matthew Koster:

But when you're starting from 10 per million, you're talking about probably increasing it to one in 10,000. So genetics play a part, but there's something else that has to stimulate or prompt the immune system to become dysregulated. And what we know from at least pathophysiologic studies is that it is really surrounding neutrophils. So what happens is you get these neutrophils that are pre-activated or primed by some pro-inflammatory mediator, responding to a stimulus, whatever that stimulus is,

whether it's infection, whether it's a reaction to a drug, or whether it's an environmental stimulus. These neutrophils then start to express proteins in their cell surface, proteinase 3, and also myeloperoxidase. And they can also release these proteins into the local environment. Those proteins are then identified by circulating anti-neutrophil cytoplasmic antibodies, ANCA, which then bind to those proteins and that results in an activation of these neutrophils. Once they're activated, they adhere to the vascular endothelium and then further release additional factors that both activate neutrophilic chemoattractants, so things that kind of stimulate the recruitment of neutrophils.

Dr. Matthew Koster:

And one of the key chemo-attractants that we are aware of that's becoming clinically and therapeutically important to something called complement 5a. When these neutrophils get primed and activate C5, a there's this feedback loop. And it's that feedback loop that ultimately leads to the kind of autoimmune and auto-inflammatory process that leads to a destructive disease. So that inflammation is amplified and continues to end up having more neutrophils traffic through tissue, into the vascular walls and causing necrosis in the vessel wall and the surrounding extra vascular tissues. So it's that process that can occur essentially in any organ system, that can lead to the local damage that's ultimately seen.

Dr. Jason Barnes:

And one question that I like to ask in this setting is what's the natural history of this disease? If someone's diagnosed with this and we don't treat it, what would we expect to happen?

Dr. Matthew Koster:

There's different levels of severity with patients with ANCA associated vasculitis. So there are patients who can have limited forms. And often these limited forms with GPA are predominantly sinonasal inflammation. Now, for those patients, if you don't catch them and don't diagnose them often, they'll get some periodic bursts of prednisone now and then when they have a flare of sinusitis that may keep things at bay. But the ongoing inflammation in the small vessels will slowly, over time, end up leading to destructive findings, which are the things that Dr. Choby And his rhinology colleagues can end up seeing the ramifications of. And so seeing the severe crusting, the mucus destruction, the perforation of the nasal septum, the cartilaginous destruction, and then ultimately even wearing a way of the sinonasal bone cavities. And so these can be pretty profound if they're not treated. That's even just with the local disease.

Dr. Matthew Koster:

Now, if there's further organ systems that are involved, for instance, the eye with like episcleritis or scleritis or orbital pseudotumor, that could lead to blindness. For patients who have lung disease, they can end up getting hemoptysis from capillaritis that can lead to pulmonary failure and require ventilation. Patients who have severe renal disease can end up developing renal insufficiency or renal failure requiring dialysis. Patients who end up having small vessel involvement in their brain can have stroke. And patients who have small vessel involvement in the peripheral nervous system can end up having irreparable motor dysfunction. And so these are conditions that before you ended up having effective therapies, in the systemic form, the non-localized form, it could be universally fatal in these patients, if they weren't adequately treated sure.

Dr. Jason Barnes:

Sure. And when someone presents to your clinic and you suspect that they have GPA, what's your initial workup?

Dr. Matthew Koster:

So initially it's really trying to understand a very comprehensive evaluation of the patient. And so for rheumatologists, our diseases really don't align with a single organ system. And so we have to essentially ask them a very broad review of systems, and we have to try to take the pieces of that information and try to put it together to say, are these things important or not? Chronic sinusitis is very common, between one and 10% of the population can end up having at some point in time. And so people who just have chronic sinusitis are not in and of themselves a high suspicion. But if they have that plus several other symptoms, then we start raising concern. But trying to assess a real head to toe review of systems, and then a very thorough investigation on exam. And for us, that requires at a minimum from an ENT standpoint, a speculum exam, an evaluation for any auricular inflammation, any chondral destruction, any septal perforation, any significant mucus crusting on speculum exam.

Dr. Matthew Koster:

But then we're also listening to their lungs, we're checking their neurologic function to make sure there's no deficits, a thorough skin exam to make sure that there's no features of small vessel vasculitis or something called leukocytoclastic vasculitis. And so that's the exam portion. And so the history, the exam are key, but then some additional features that are helpful in our evaluation are laboratory investigations and imaging studies. So some key laboratory investigations include ANCA serologies, and there's two main ways that labs end up testing this. One is through checking, C-ANCA and P-ANCA. That's done through something called immunofluorescence, where they titrate it out in wells to look for positivity. And then there's their confirmatory antibodies that are called proteinases 3, PR3, and myeloperoxidase, MPO. So for patients with GPA, most commonly they'll end up having C-ANCA with PR3 antibody. That's going to be in the majority of cases and often more to the realm with 80 to 90% of cases that have positive ANCA serologies. Whereas some may have P-ANCA and myeloperoxidase antibody.

Dr. Matthew Koster:

The patients who have limited disease may not have those antibodies to be present. So you have to maintain a high level of suspicion. We end up checking inflammatory markers, which are often elevated. We check regular CBC with differential to look for any features of thrombocytosis or decreased hemoglobin. Inflammatory markers are very often positive in these patients at high levels, in some circumstances, with sed rate and C-reactive protein. And then also it's very important to look at renal function with creatinine and urinalysis to look for their blood in the urine or protein in the urine. That would indicate renal involvement. Beyond that, imaging studies, sinus imaging with CT scan can be helpful to assess for the burden of disease if present. And then what I recommend, even if patients are asymptomatic, is that a minimum to get a chest X-Ray, but often a high resolution, non-contrast CT scan can pick up some subtle findings of abnormalities, such as ground glass opacities that may not be identified on chest X-Ray, which can typically pick up features of things like nodularity, or adenopathy in the hilum or mediastinum.

Dr. Jason Barnes:

And Dr. Choby, what's your workup when you see these folks in clinic?

Dr. Garret Choby:

So oftentimes they will come to us with a sinus CT scan. And this is really important in their workup. There can be a number of nonspecific findings, such as mucosal inflammation and general crushing. But some tip-offs can be, again, septal perforation, which you can pick up on a CT scan, or a more destructive process in the mucosa in the bone of the lateral nasal wall can be fairly characteristic of GPA.

Dr. Garret Choby:

And then we also do a nasal endoscopy in all of these cases. Dr. Koster and I share a lot of patients together and I will directly share these pictures we take with endoscopy with him and characterize to what degree their nose looks like a classic case of GPA. In addition, we have a low threshold to biopsy these patients. And that can either be the active inflammation around a septal perforation or active destruction in an area of the lateral nasal wall. These are also not all the time very specific. They may simply come back as general inflammation. But the tip off for GPA in a biopsy of the nasal cavity would be vasculitic changes usually with a neutrophil predominant vasculitis, as well as necrotizing granulomas in giant cells, would be the more typical findings specific for GPA, but are not present in specificity in a number of these samples.

Dr. Jason Barnes:

Sure. I know in rhinology clinic, you're more likely to use a rigid endoscope. Do you often use a flexible scope to evaluate the larynx? Is there usefulness in that?

Dr. Garret Choby:

We oftentimes will use a flex scope to take at least a cursory look at the larynx. However, if these patients have any symptoms of airway difficulties, a history of intermittent stridor, or noisy breathing, then I will certainly get involved on, my colleagues in laryngology or head neck, and have them do a more formal laryngeal exam, and potentially even a subglottic exam in the clinic to evaluate for subglottic stenosis.

Dr. Jason Barnes:

Dr. Koster, we've talked about a lot of different symptoms in the workup, including lab studies and possible biopsy. How do you make an official diagnosis of GPA?

Dr. Matthew Koster:

Yeah. I'd say that there's different levels of certainty when you're making a diagnosis of GPA. Certainly if you have classical features such as ENT involvement with sinonasal destructive features, pulmonary involvement with nodularity plus other organ manifestations in a patient with positive ANCA serologies, and a biopsy that confirms disease in some location, whether that be sinuses, kidney, skin, lung, et cetera, that's a very conclusive case. And I think everybody will feel comfortable with that.

Dr. Matthew Koster:

Then there's patients who have the appropriate clinical characteristics and they may have positive ANCA serologies, but their biopsy is nonspecific or negative. That's still something in which I think we feel comfortable with making the diagnosis. And I think that from an ENT education standpoint, you need to know that often, as Dr. Choby mentioned, these biopsies may be nonspecific. That doesn't mean it's not

there. And so you still have to have a high threshold for suspicion to end up determining whether treatment's required.

Dr. Matthew Koster:

For patients who have symptoms that are suspicious for this disease, but they have negative ANCA serologies, and nonspecific or negative biopsies, that's where you have to use your judgment to look for other etiologies that may mimic these findings. And one of the things that you really want to make sure that is not present is infection. Because immunosuppression is not going to make that better and can make things complicated. For patients who just have positive ANCA serology and minor ENT findings, we would probably just observe and not end up making that diagnosis unless other organ systems were affected that could end up increasing our suspicion and threshold for diagnosis.

Dr. Jason Barnes:

And in preparing to talk to you about this, I heard about the Chapel Hill Consensus. Can you talk a little bit about that?

Dr. Matthew Koster:

Sure. So there have been different ways for people to describe the different primary vasculitides. And by primary vasculitides, we mean where the vasculitis is the disease itself, as opposed to a secondary vasculitis where it's caused by something. So for instance, like hepatitis B associated polyarteritis nodosa, that's a secondary vasculitis. So this was a consensus group that initially met in the early 1990s. And then they revised their nomenclature in 2012, which is where they changed the name to GPA, as opposed to Wegener's. And that paper, that position paper, goes through the individual primary vasculitides and uses the appropriate language. And then also highlights the organs that are commonly affected and what labs, imaging, and biopsy studies should be expected in cases for this. And so for people who have an interest in vasculitis of any type, from any field, I think that that's a reasonable read to get some additional information.

Dr. Jason Barnes:

Great. We've talked about presentation, workup, evaluation, that kind of thing. I'd like to move on next to treatment. And I understand we can talk about it from a rheumatology side and an ENT side. Dr. Koster, do you want to start with how you treat folks who present with GPA?

Dr. Matthew Koster:

Sure. So the first thing again is trying to understand what organ systems are affected. So often we end up trying to stage these patients as far as trying to identify where things are at the beginning, so that we can one, determine their severity and two, determine what things need to be monitored to look for efficacy and treatment response. For patients who have mild to moderate sinonasal abnormalities or limited GPA, we'll typically treat those patients with moderate doses of steroids, 20 to 30 milligrams with a taper. And then often these patients specifically patients who have C-ANCA, PR3 positivity will often relapse with recurrence of sinonasal abnormalities with a reduction in the steroids. So we'll often end up employing another medication, like a disease modifying agents, such as Methotrexate, which is the most common. Other moderate level immunosuppression, such as Azathioprine or less commonly Mycophenolate, could be used in those circumstances.

Dr. Matthew Koster:

For patients who have systemic disease in which there's severe involvement, whether that be renal, neurologic, either central or peripheral, cardiac, or pulmonary involvement, those patients often require what we call induction therapy, which historically has been with Cyclophosphamide but now is more commonly with Rituximab, which was approved for these conditions back in 2010, and has gained a lot of increase utilization since that time. For patients who have very severe sinus disease, in which they've either failed initial treatments, or they have severe destructive findings, we will sometimes treat those patients also aggressively either with things like Cyclophosphamide or Rituximab for induction therapy. And that's often guided by our ENT colleagues, as far as how bad they see things when they're evaluating it, or are these patients failing to respond to the therapies that are common or typical at the lower level.

Dr. Jason Barnes:

And Dr. Choby, when you're evaluating these patients, how do you decide how to treat them and what treatment options you offer them?

Dr. Garret Choby:

I would say that our, our initial role in treatment is helping with the diagnosis in many cases. And that's where things like examination and communicating those findings as well as potentially offering a biopsy. I will also mention briefly that even though the biopsy is nonspecific in many cases, it can also be helpful to rule out other disease processes. As Dr. Koster mentioned, you'd hate to be treating someone for a limited form of GPA when in fact something else was brewing. And one of those things can be, again, a lymphoma or a midline destructive lesion. Sometimes a simple biopsy will help to rule out those other processes and allow treatment with immunosuppressive medication for GPA. We'll also do things in the nose to help to diminish crushing. That can either be topical saline rinses or frequent debridements in the clinic. We will occasionally add a topical Mupirocin to a rinse, which has been shown to decrease crusting and Staph aureus load in some cases.

Dr. Garret Choby:

And there's also some low level evidence that occasional or intermittent use of low levels of antibiotics, such as Bactrim can be helpful again, largely to diminish crusting in these patients. The bigger question that arises oftentimes is they can be quite symptomatic from a sinus standpoint. And when you will, or when you will consider performing sinus surgery, and we look at this very carefully because these patients have a very, very high chance of scarring and closing on their sinuses postoperatively, because you may be creating injury in a field that is otherwise very inflamed. So we really hold off on offering sinus surgery to these patients until their disease is very well controlled. And that's usually in conjunction with our rheumatology colleagues like Dr. Koster. We often would like to have them stabilized and not needing any rescue steroid medication for about six months or so. And also ensuring that their inflammatory blood levels have also normalized, things like the ESR and the CRP have been under good control for a long period of time.

Dr. Garret Choby:

And then we'll discuss with our rheumatology colleagues, the optimal dosage of things like Rituximab and steroids in the perioperative period. I'll also mention that with saddle nose deformities and large septal perforations, our colleagues in facial plastic surgery are oftentimes involved and they also, again, take a similar consideration when they may offer the patient reconstruction with things like our rib graft, because of course they don't want that to be affected by an ongoing inflammatory process.

Dr. Jason Barnes:

And Dr. Koster, how do you monitor these patients? How do you follow up with them and how do you counsel them on their prognosis?

Dr. Matthew Koster:

So for patients who you end up having visible abnormalities, for instance, patients who have predominant skin vasculitis. That is very easily and visibly identified as far as improvement. For patients who have lung disease, we monitor them often by pulmonary function testing, to see if they have improvements in those parameters, as well as by imaging like resolution or decrease in nodularity or ground glass opacities. If they have renal dysfunction, then often watching the creatine improve or watching the urinalysis have decrease or resolution of hematuria or proteinuria.

Dr. Matthew Koster:

And then of course, if they've had elevated inflammatory markers, like sedimentation rate or C-reactive protein, watching those trend down to normal is ideal. We do, in some patients, depending on how positive or if positive their ANCA serologies are, that can be used in some circumstances. Patients may go from strongly positive to negative with treatment. And those patients seeing an increased swing with the ANCA serologies can forecast or be seen in the context of a flare. But there are some patients in which those ANCA serologies have no bearing on their disease activity and may remain positive even if they're in clinical remission.

Dr. Matthew Koster:

For our ENT colleagues, it's extremely helpful because while I can look at scans, I can do a thorough exam, I can't look all the way back in the sinuses or down into the airways and the subglottic region. And so often when we're following these patients, which there's a lot of intense visits at the beginning, and then once they're stabilized, less frequent visits, maybe every two to four months afterwards, is to periodically have the ENT physicians, if they had predominant sinus symptoms to begin with, to see them back and do periodic scopes to see if things are looking better. Because they can correlate as well to say whether or not the tissue seems to be healing or if there's active disease. And so with our multidisciplinary clinics here, we're often able to have that same day, where they may be able to see the ENT person earlier in the morning and then see us later that morning or in the early afternoon, so that we can have an ongoing discussion of what things look like.

Dr. Jason Barnes:

Well, this has been a super helpful conversation. Dr. Koster, thanks so much. Before I provide a summary of what we've talked about. Is there anything you Dr. Koster, Dr. Choby, would like to add?

Dr. Garret Choby:

I'll just mention that this is a really challenging disease, and it's really awesome to work with experts like Dr. Koster who have a real interest and expertise in this disease process. And we can learn a ton from each other when we work together. And it's been very rewarding.

Dr. Matthew Koster:

I would just echo that. I think the important thing is that when you're dealing with multi-system rare diseases that can be complicating both in the diagnosis and management, is to really get a core group of

people who had experience with these diseases and are able to communicate effectively, to the best needs of the patient.

Dr. Jason Barnes:

Well, thank you all so much for being here. I'll now provide a quick summary of what we've talked about. GPA, or granulomatosis with polyangiitis, is a rheumatologic disease primarily, but it will typically manifest with multiple episodes of chronic sinusitis and other manifestations such as kidney, lung, or neural issues.

Dr. Jason Barnes:

Some of the ENT manifestations particularly are chronic rhinosinusitis, but we can also see things like saddle nose deformity and subglottic stenosis, as well as otitis. Initial workup includes ESR and CRP, with ANCA, C-ANCA being more frequently positive, but P-ANCA can also be positive up to 10%. And a diagnosis is contingent on the clinical picture being brought together and biopsy can have a role in here, which is where ENT can come into play.

Dr. Jason Barnes:

From an ENT side, treatment can include nasal rinses or other treatments that are consistent with chronic rhinosinusitis, but Mupirocin can also be helpful, as can Bactrim from a systemic antibiotic standpoint. And then from a rheumatologic side, there are a lot of systemic therapies, including steroids, Methotrexate, Rituximab, and Azathioprine. Anything else I left out or it's worth mentioning?

Dr. Garret Choby:

No, I think that was very thorough. Thank you, Jason.

Dr. Matthew Koster:

Yeah. Thank you, Jason.

Dr. Jason Barnes:

Thank you.

Dr. Jason Barnes:

I'll now go into a time of questions before we end this episode. As a reminder, I'll ask a question and then wait for a few seconds and then provide the answer. So the first question is what is the pathology of GPA? GPA, a small to medium vessel vasculitis. And if you take a biopsy, it would show necrosis and granulomas with vasculitic inflammation. And remember, this is predominantly neutrophil driven.

Dr. Jason Barnes:

The next question is, what are the common laboratory findings when you test for GPA? Lab workup can involve a lot of things, but when we get ESR and CRP, that will likely be elevated. And when we do ANCA studies, C-ANCA is more likely to be positive. And these patients are almost always positive from an ANCA standpoint, but that's not always the case.

Dr. Jason Barnes:

What is the most common first manifestation of GPA? One of the most common first manifestations of GPA is sinusitis, or chronic sinusitis, which is why this can be seen in ENT clinic with so much regularity.

Dr. Jason Barnes:

And finally, what are some treatment options for GPA, including systemic and ENT or sinonasal related treatments? From an ENT side of things, treatment can involve steroid rinses, systemic antibiotics, including Bactrim and topical antibiotics, including Mupirocin. From a systemic standpoint, steroids, Methotrexate, Rituximab, and Azathioprine includes some of the more commonly used treatments in these patients.

Dr. Jason Barnes:

Thanks so much and we'll see you next time.