Eosinophilia in Patients with Asthma: A Sign of Eosinophilic Granulomatosis with Polyangiitis (EGPA)? - Question and Answer

Overview

Welcome to this question and answer interview with Michael Wechsler, MD. In this activity, Dr. Wechsler answers common questions physicians have about the diagnosis, prognosis, and treatment of EGPA. This Q&A addresses topics such as the role of ANCA in diagnosis and prognosis, the clinical signs and symptoms of EGPA, clinical features associated with poor prognosis, specialists who may see patients with EGPA presenting as another disorder, and treatment response, escalation, and monitoring.

Content Areas

- Clinical Features, Common Presentations
- Five-factor Score and Prognosis
- Treatment Clinical Pearls

Target Audience

This activity is intended for allergist/immunologists, rheumatologists, pulmonologists, hematologists, dermatologists, cardiologists, EENT specialists and other clinicians involved in the care of patients with EGPA.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Discuss the clinical signs and symptoms that support a diagnosis of EGPA
- Describe the clinical progression of EGPA
- Classify patients' risk based on disease activity and the presence of ANCA
- Select an appropriate therapy for EGPA based on patient's disease activity and characteristics

Faculty

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The estimated time to complete the activity is 0.75 hour.

This activity was released on June 30, 2020 and is eligible for credit through June 29, 2021.

Contact Information

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Are there any biomarkers that are specific to EGPA or that are especially helpful for making the diagnosis?

Dr. Wechsler: There are several key biomarkers that I utilize clinically for the management of EGPA. First and foremost is the E of EGPA, which is the eosinophils. And that is a really important biomarker that helps establish a diagnosis of EGPA and can also be useful in terms of tracking disease activity. Higher levels of eosinophils are associated with increased disease activity.

Other things that I follow include just nonspecific biomarkers of inflammation, including C-reactive protein and the erythrocyte sedimentation rate. And those both can correlate with disease activity as well. They both correlate with systemic inflammation in general. Lastly, I generally tend to follow antineutrophil cytoplasmic antibody levels or ANCA levels. These have been shown to weakly correlate with disease activity in people who are ANCA-positive. Only about 40% of patients tend to be ANCA-positive in the EGPA population.

What signs and symptoms are best for recognizing vasculitis?

Vasculitis can occur in any organ system, and so it's important to do a broad evaluation of your patients. Patients can present with pulmonary manifestations and they can present with asthma or cough or pulmonary infiltrates. They can present with cardiac manifestations and they can be short of breath and may have evidence of cardiomyopathy or myocarditis. Patients can present with rash and could have dermatologic manifestations. It's important to evaluate rash. Patients can also present with neuropathy, numbness, tingling, weakness, that's going to occur in a "stocking-glove" distribution and can occur anywhere in a given patient. They also present with central nervous system disease. I also look for any other neurologic involvement, muscle weakness, and I also tend to evaluate for kidney involvement as well.

How likely am I to ever see a case of EGPA?

Well, it's estimated that there are about 5,000 people in the United States who are affected by EGPA, but I think that number is still is probably an underestimate and there are probably many other patients with EGPA. The people who are most likely to see patients with EGPA include pulmonologists and allergists, as well as rheumatologists, but there are a variety of different specialists who may encounter patients with EGPA. These include gastroenterologists who might see GI manifestations, ENT doctors who may see the sinus disease and or nasal polyps. Hematologists may see it because of the presence of eosinophilia. Similarly, infectious disease doctors may also see it because of the presence of eosinophilia. The likelihood really depends on your practice.

There is a little bit of a predilection for northern latitudes. And so maybe physicians who are in the north may see these patients more than people in the south, and certainly the degree of specialization that you may have in your practice. It's likely that you have seen some of these patients. You may see them if you've been in primary care or in the emergency room, and it's important to be able to recognize the signs and symptoms of EGPA.

Can patients have EGPA and be ANCA-negative?

Approximately 40% of patients with EGPA are ANCA-positive and studies have shown that this ranges from 10% to 40%. Most patients who present with these antineutrophil cytoplasmic antibodies have specificity for p-ANCA perinuclear ANCA pattern with myeloperoxidase positivity, but you can have p-ANCA positivity patients as well.

Because only 40% of patients tend to be ANCA-positive, certainly the vast majority of EGPA patients

will be ANCA-negative. It's helpful to look for ANCA-positivity because it really changes potential treatment approach. And there may be specific organ systems that are more likely to be involved. For instance, ANCA-positivity is associated with alveolar hemorrhage, glomerulonephritis, and peripheral neuropathy. And ANCA negativity occurs oftentimes with cardiomyopathy. It's important to evaluate for it because it can help a little bit with prognosis, but also can help guide treatments. You may consider more of an antibody-mediated strategy, for instance, using a drug like rituximab in ANCA-positive patients.

Can ANCA status change in patients with EGPA?

ANCA status can change in patients with EGPA. Patients can have positive titers and negative titers, and this can change over time. There have been some data published in the Mayo Clinic, which have suggested that ANCA-positivity can correlate with disease activity, but this hasn't been replicated in larger groups of patients in different studies.

What would you consider hypereosinophilia?

Hypereosinophilia can be considered in any patient who has high levels of eosinophil counts in the blood, and there's a pretty broad differential for hypereosinophilia. When I say high levels of eosinophils, you're talking about more than 1,000 eosinophils for more than 10% of the white blood cell counts. And the differential diagnosis is pretty large. You know, certainly we think about allergic disorders and drug reactions to, I don't know, a variety of different medications, including allopurinol, minocycline, different antidepressants, different antibiotics, allergic conditions like asthma and atopic dermatitis. Infections have been associated with hypereosinophilia, as well, particularly parasitic infections, schistosomiasis, filariasis, trichinella, strongyloides infections, coccidioidomycosis, histoplasmosis, aspergillus, HIV of wide variety. There are a variety of immune deficiency states associated with hypereosinophilia, as well, including hyper IgE syndrome, DOCK8 deficiency, amongst others. There are autoimmune conditions like sarcoidosis, inflammatory bowel disease, other connective tissue disorders. And then there are the more rare hypereosinophilic syndromes, including idiopathic hypereosinophilic syndrome, which can manifest as both a myeloproliferative or a lymphoproliferative variant. And then most of these caged patients have nonspecific hypereosinophilia. In addition to those, there are organ-specific entities including chronic eosinophilic pneumonia, which can be characterized by eosinophilia. Then eosinophilic gastrointestinal disorders can be characterized by eosinophilia. And then other entities, including hypoadrenalism, radiation exposure, cholesterol emboli. You need to think very broadly when you see patients with hypereosinophilia. But really, when I'm thinking about EGPA and hypereosinophilic syndromes, I'm thinking about people who have eosinophilia levels greater than 1,000.

Is EGPA a chronic or acute presentation?

EGPA is more of a chronic disease, but it can certainly present acutely. And, oftentimes, still present in a basic pattern where patients will have a long history of asthma and allergies and then may develop more of an allergic diathesis. And it isn't until they reach the vasculitic stage where they will present as EGPA. But it can be very hard to make a diagnosis and people need to recognize the eosinophilia tied into the asthma, and the pulmonary infiltrates to make a diagnosis. When they present acutely, they often present with neurologic manifestations or cardiac manifestations, sometimes renal manifestations or GI manifestations, or they can just present with one of the exacerbations of the underlying pulmonary disorder with an asthma exacerbation or pulmonary infiltrates that presents as pneumonia.

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What is a typical clinical picture for a patient with EGPA?

The clinical picture of patients with EGPA really is quite variable. In general, we think about several key manifestations, and those include asthma and eosinophilia as well as chronic rhinosinusitis with maybe nasal polyps and pulmonary infiltrates. But on top of that, what distinguishes EGPA from eosinophilic pneumonia—chronic eosinophilic pneumonia—is the presence of extra pulmonary manifestations. I'm looking at patients who don't just have the asthma, the pulmonary infiltrates, the synosis along with the eosinophilia. But we have other organ manifestations that may include GI tract involvement present with abdominal pain or ischemic bowel. Patients who present it with skin manifestations, with palpable purpura or skin nodules or urticaria livedo reticularis. Or they may present with vasculitis that may manifest as deep vein thrombosis or arterial thrombosis, or they may present with the neurologic manifestations that we've talked about that includes neuropathy, numbness, weakness, or neurosensory, hearing loss. All those are some of the key manifestations that they can present variably over time in our patients with EGPA.

What patients are most likely to have unrecognized or a misdiagnosis of EGPA?

Patients with EGPA often go unrecognized and unnoticed because it's hard for physicians to tie together all the different manifestations that a patient may have. And that really bespeaks the challenging journey that patients have in terms of achieving a diagnosis. They may present to an ENT doctor with sinus manifestations or nasal polyps. But that doctor isn't thinking about the extra pulmonary, extra ENT manifestations. They may present to a pulmonologist with pneumonia, pulmonary infiltrates and asthma or wheezing, but the pulmonologist may not ask about the rash that's going on or may not tie those 2 things together. Similarly, the patient may present with GI manifestations and the gastroenterologist may focus solely on the GI manifestations without anything else, or they may present to the neurologist with neuropathy and foot drop and it isn't until they evaluate for eosinophilia and start asking other questions.

It can take a while to achieve a diagnosis. The key thing is that if you see any patient, you want to do a broad review of systems to see what else could be going on. To give you some clue into the insight of what could be going on and to evaluate for the manifestations of EGPA.

What is the difference between eosinophilic asthma and EGPA?

Eosinophilic asthma is an entity in which patients present primarily just with asthma symptoms, shortness of breath, cough, wheezing and airflow obstruction in the context of high levels of blood or sputum eosinophils. And they may just have only eosinophilic asthma. When one thinks about patients with EGPA, however, they don't just have the eosinophilic asthma, almost all those patients do have eosinophilic asthma. But on top of that, they have other manifestations that include pulmonary infiltrates, sinus disease, and then vasculitis in one or more end organ. So that can involve the heart, the GI tract, the kidneys, the skin, the nervous system, and a variety of other entities and organ systems. When I think about the difference between EGPA and eosinophilic asthma, I'm thinking about what happens outside of the lungs. And that really gives me a clue in terms of making a diagnosis of EGPA.

Is a biopsy needed to confirm EGPA? When should I do one? And what tissue is the most sensitive to detecting granulomas? Can I use a bronchoalveolar lavage?

The gold standard for diagnosis of EGPA is the presence of vasculitis on a biopsy of any specific tissue. And you can do a biopsy of any organ that is involved, and that can be from the GI tract, to the lungs, to the nerves, to the muscles, to the skin. Is it necessary to do a biopsy? Well, probably not. In most cases, if you can tie together the complex manifestations of asthma in the context of eosinophilia, as well as the presence of pulmonary infiltrates, sinus disease, and then if you see a rash, if you see a patient who has neuropathy, if they have the other manifestations of EGPA, you don't necessarily need to do a biopsy. EGPA is a clinical diagnosis, you don't necessarily need to have tissue to make that kind of histopathologic diagnosis, although that can be helpful in establishing a diagnosis in many patients.

I was also asked about whether or not one can do a BAL or a lung biopsy, that can be a surrogate. Well, a bronchoalveolar lavage gives you insight into lung tissue eosinophilia and can be helpful, but it doesn't necessarily clinch the diagnosis because that may represent chronic eosinophilic pneumonia as well. In terms of making a diagnosis, one often doesn't see vasculitis on a transbronchial biopsy, and one generally needs a larger biopsy forceps to help make a diagnosis. And that would be done through a VAS or a larger biopsy taken from the lungs.

Are there certain patients, populations, or ethnicities that are at higher risk for EGPA?

EGPA can be seen across the spectrum of ethnicities and across a broad group of patient populations. It's seen in Blacks, in Whites, in Hispanics and other minorities. It's seen in Asians, as well as in Caucasians. I don't think of any specific ethnic group or any specific heritage, in terms of coming up with a diagnosis. That being said, there is a little bit of a predilection for northern latitudes. People who are living in northern latitudes are more likely to have a diagnosis of EGPA than people at lower, more southern latitudes.

Is ANCA important for prognosis?

ANCA can help a little bit with prognosis. Again, ANCA can identify patients who have alveolar hemorrhage, glomerulonephritis, peripheral neuropathy. If ANCA-negativity doesn't exclude EGPA, as I mentioned, it can be associated with cardiomyopathy. It really reflects underlying vasculitis, and patients who tend to have the vasculitic component of EGPA may have a worse prognosis. What really reflects prognosis is older age, presence of central nervous system, cardiac, renal, and GI manifestations. The more of those factors that you have, the so called 5 factors score, the worse the prognosis an individual has.

What one question do patients ask most often after diagnosis, or what one thing would you want to make sure they understand about EGPA at diagnosis?

The most important thing I tell my patients is to be vigilant for any new signs or symptoms of EGPA. I want my patients to be on the lookout for any new neuropathy or worsening neuropathy, any new GI manifestations or skin manifestations. If you don't intervene quickly and treat those patients quickly and aggressively, then they could have potentially, long-term, more organ damage that may go on chronically. The earlier you intervene, the more likely you are to achieve success in terms of managing their underlying disease.

At diagnosis, patients have a whole variety of different questions that they want to ask. They want to know what their prognosis is. They want to know whether their kids are at risk. They want to know whether there are treatment options. They want to know side effects of treatment. It's important to have a good understanding of the disease state and all of these different factors in talking to patients so you can

convey to them and reassure them that they should be okay if they're vigilant and they should be okay if they get their disease under control and in remission. The major goals of therapy is something else they ask about, and that includes prevention of relapses and induction of remission. These can be achieved in most patients with corticosteroids, and sometimes require other corticosteroid-sparing therapies.

What are some of the most common or problematic complications in patients with EGPA?

The most common problems in patients with EGPA relate to the occurrence of relapses and/or side effects for medications. Our major goals in management include prevention of relapses and prevention of side effects from medications. In terms of side effects of medications, glucocorticoids are often the drug of choice, and they're associated with cataracts, glaucoma, osteoporosis, hypertension, weight gain, mood swings, and a variety of other different complications. We want to try to prevent those. In terms of the relapses themselves, they can be associated with worsening respiratory function, acute asthma attacks, occurrence of worsening neuropathy, amongst others. We want to try to prevent those relapses from occurring.

Once I have a confirmed diagnosis, what referrals should I consider?

Once you have a diagnosis of EGPA, referrals really depend on the specific organs that are involved. In general, it's helpful to have a pulmonologist onboard or an allergist onboard to help manage one's asthma and/or the pulmonary infiltrates. It's generally worthwhile to have a rheumatologist onboard to help with disease modification, disease medication-sparing therapies, because oftentimes rheumatologists have good insight into some of the immunosuppressants that are utilized. Many patients have sinus disease and ENT manifestations, so it's worthwhile to see an ENT specialist.

Otherwise, it depends on the organ system that's involved. Cardiologists are involved with patients who have cardiac involvement. Gastroenterologists are involved with patients who have GI involvement. Neurologists can help with some of the pain, as well as the diagnosis, for patients who have gotten neuropathy. Dermatologists can be involved as well. Then for patients who are on long-term corticosteroids, oftentimes they need to see an endocrinologist to help manage the endocrine manifestations of long-term corticosteroid use.

Once I start treatment, how long until I can expect to see a response or clinical improvement?

Clinical improvement occurs in patients with EGPA almost immediately when you implement corticosteroids and other steroid-sparing therapies, and those are the major goals, really, to reduce the occurrence of relapses, to minimize symptoms, and to prevent the side effects of other therapies, including glucocorticoids. We generally see a significant reduction in eosinophil counts very early on, and that can also benefit patients who have asthma manifestations or pulmonary infiltrates. Usually within days, patients will have significant improvement in their outcomes. But not all patients respond quite so quickly, and those patients need either other steroid-sparing therapies or other add-on therapies that may be helpful in terms of mitigating disease inflammation.

How long should I give for corticosteroids to have an effect, and what would be the next treatment to try if I don't see improvement?

Generally, you want to see efficacy with corticosteroids within a few weeks, and if there's no reduction in eosinophil counts, you need to move on even more quickly. But what we're looking for is reduction in symptoms. I generally treat my patients with

corticosteroids for months and looking for early response. When patients don't respond early, within days to even weeks, then I consider adding on corticosteroid-sparing therapies.

What does an ideal treatment response look like?

Ideal treatment response really can be reflected both in terms of blood work as well as symptom abrogation. You generally want to see a significant reduction in eosinophil count in the blood, improvement in sedimentation rate, C-reactive protein, as well as turning ANCA-positive patients into ANCA-negative patients. And then you also want to see significant symptom improvement. It depends on the symptoms that are involved. Patients who have rashes, rashes should go away pretty quickly. People have asthma symptoms or pulmonary infiltrates, those should go away pretty quickly. People who've got GI symptoms, abdominal pain, neuropathy, we like to see those improve, although oftentimes the neuropathy can take longer to resolve.

If a patient improves and responds to treatment, what kind of follow-up monitoring should I do and how long should I continue monitoring them?

In general, I follow my patients pretty closely. Early on in their management, I'll see them on a monthly basis and then I might move to every 2-3 months and then every 6 months. It really depends on the disease manifestations. I will follow pulmonary function testing and eosinophil count, sedimentation rate, and C-reactive protein. People who have got cardiac involvement, I'll follow them serially with either echocardiograms or cardiac MRIs. People who've got neuropathy, I might follow them longitudinally as well with EMGs and nerve conduction studies to see if there's any improvement going on. It is important to follow these patients quite closely. However, I give all these patients my phone number and tell them to call me and to be really vigilant for any new signs or symptoms of active disease.

What steroid-sparing therapies do you consider and when do you consider them?

I consider steroid-sparing therapies in patients who continue to relapse or in patients who fail to respond to initial treatment, after treatment induction, or if corticosteroid dosing can't be tapered, if I can't get down to lower doses of corticosteroids. And there's a wide variety of different therapies that I consider in these patients. I consider, initially, for induction treatments, drugs like cyclophosphamide, on top of glucocorticoids to induce remission in our patients, and then I think about more chronic steroid-sparing options, including drugs that are immunosuppressants, such as azathioprine, methotrexate and occasionally interferon gamma, interferon alpha.

But in many patients who have more eosinophilic disease in patients who have asthma, in particular, those patients I consider anti-IL5 treatment with drugs like mepolizumab. Mepolizumab is an anti-IL5 monoclonal antibody that's been shown to reduce relapses and help induce remission in patients with EGPA in large controlled studies and has helped to facilitate corticosteroid withdrawal safely, reducing corticosteroid dosing by over 50%. One other therapy that I consider, particularly in ANCA-positive patients, is rituximab, and that helps prevent antibody production including antineutrophil cytoplasmic antibodies or ANCA.