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Patient with Uncontrolled Asthma While on a Biologic: Clinical Consults

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Dr. Panettieri:
Drs. Corren and Wechsler, uh, welcome. Uh, good to, uh, to be discussing these cases with you again. And to all our colleagues who submitted these dif – difficult cases to review, we really appreciate it. Now, today’s case, is a 63-year-old male with allergic rhinitis, mixed eosinophilic neutrophilic asthma, and the patient has severe asthma. He’s on prednisone 10 mg daily, tiotropium, budesonide/formoterol 160/4.5, and montelukast. Mepolizumab was added and it helped, but he still had three flares a year and no change, no change in the chronic steroid use. So, the steroid burden was substantial. An update that was obtained while the patient was on mepolizumab showed that eosinophils didn’t go to zero but did significantly decrease. They went to under 100 but not to zero. So, the question here is there’s improvement, but the patient’s biomarker and the pharmacodynamic biomarker of eosinophils wasn’t completely obliterated. So, given this case, uh, Dr. Corren, how does mixed eosinophilic neutrophilic asthma differ from eosinophilic asthma from a clinical and treatment perspective?

Dr. Corren:
Ray, in order to answer that question, I think it would be useful to first define what we’re talking about when we say eosinophilic or neutrophilic or mixed eosinophilic and neutrophilic asthma. Eosinophilic asthma, as we all know, we base upon a, a peripheral blood count looking for eosinophils with a cutoff of 150 generally indicating that eosinophilic asthma’s present. Uh, when it comes to neutrophilic asthma, we can’t really base this on the blood count. In other words, an increase in blood neutrophils does not indicate what’s going on in the airway, and to make this distinction, we generally rely upon a sample of induced sputum where, generally speaking, we look for 60% of the cells on that slide should be neutrophils in order to make this categorization. And a mix of the two entities would suggest either a mix of eosinophils greater than 2 or 3% plus 60% neutrophils on the sputum slide or that number of, of neutrophils present in sputum with an increase in blood eosinophils, as we’ve already discussed. So, the question is why would somebody have a mixed picture? Part of it may rely upon the fact that people can have other disease entities, other comorbid conditions that could potentially cause neutrophils to arise in the airway. Uh, things like gastroesophageal reflux, um, acute or recurrent bronchial infections might predispose or lead to this development, or chronic sinusitis. So, these are some of the things we have to consider when approaching patients that have been diagnosed with this entity. Um, when we consider these other possible comorbid conditions and we’re faced with a patient who doesn’t have a complete response to a type 2 inhibitor, then we might want to consider some possible therapies directed at the neutrophilia itself, and there’ve been a number of different trials as well as many anecdotes where patients with so-called neutrophilic or mixed eosinophilic neutrophilic asthma have been treated with macrolide antibiotics. There’s probably more data to support this class of medications than any other, and this would include both azithromycin and clarithromycin, typically taken for

a period of 3-6 months, and in many of these patients, there is a robust response to this therapy.

Dr. Panettieri:
Great points, Jonathan. That's, uh, really spot on. Um, so Mike, you know, what are some of the reasons that the patient may not respond to mepolizumab? Uh, would you want to also comment at that point is what would you do in this case to reduce the chronic oral corticosteroid burden that the patient's experiencing?

Dr. Wechsler:
Yeah, so, uh, I, I think it's really important to evaluate, in terms of response, of whether or not the patient has other comorbidities that could still be going on in these kinds of patients. Could he have ongoing, uh, uh, reflux disease? Could he have ongoing chronic rhinosinusitis? Uh, could there be, uh, some vo - elements of vocal cord dysfunction? What about aspiration? Could that be an issue? So, often times, we find these patients who've got severe disease, particularly patients who have a mixed, uh, eosinophilic-neutrophilic phenotype, they've got some other factor going on. Another issue is is are they completely adherent to their therapies? And that's another important factor. Um, and so that would be the first thing that I would do. Now, uh, it is a little bit unusual for patients who, um, are on, uh, anti-IL-5 therapy to not have their eosinophil counts go significantly below 100, um, and that might reflect the heterogeneity of response to these therapies and the pharmacodynamics and the, and, and pharmacokinetics, uh, in specific individuals. Um, and that's why in other disease entities, like in eosinophilic granulomatosis with polyangiitis, we tend to give a higher dose, actually, of, of a drug like mepolizumab. In terms of what to do next in terms of getting the patient's corticosteroids down, uh, I think it's important to do it very slowly, and sometimes, uh, what happens is, is, um, uh, physicians and patients, uh, either go too quickly or they don't go quickly enough, uh, in certain circumstances, and they'll, attribute a failure, uh, of tapering to, uh, perhaps some mild, ongoing symptoms. So, I tend to go very slowly. So, someone who's on 10 mg a day, I'd go down to 9 mg a day, as opposed to down to 5 mg a day as some, some others might do, and go down very slowly in 1, 1 to 2 mg increments, and sometimes that achieves benefit. There might be other reasons for this patient's failure and it might relate to the underlying pathophysiology of the asthma, and in those circumstances, we need to wonder whether or not there could be some other mechanism that's at play. Jonathan mentioned, uh, potentially that there could be ongoing infection that could be, uh, ongoing and could, uh, addition of a macrolide antibiotic be beneficial? I wholeheartedly endorse that approach, uh, as well. So, I, I think a combination of recognizing and looking for comorbidities, uh, try to understand the pathophysiology, and getting a better sense of what the endotype is. And maybe for this person that we don't have the right drugs available as of yet, and maybe we need some other newer therapies that are on the horizon or in development.

Dr. Panettieri:
Great points. Um, Mike, I think, uh, you really, uh, gave us, uh, good insight in the case. You know what's a little surprising to me, in this case the patient's getting two World Cup drugs to wipe out eosinophils – I'm talking about oral steroids and an anti-IL-5 – and despite that, this patient's eosinophils are not, are, are not zero. Uh, isn't that surprising? And I really like the idea about adherence and whether there's challenges to adherence. Do you want to care to comment on that, Mike? And then Jonathan, your insight.

Dr. Wechsler:
Yeah, so, uh, the production of eosinophils is variable in, uh, different individuals and there may be a variety of different mechanisms that result in eosinophilia. Uh, whether it's, uh, straight from the bone marrow or whether there are sometimes some T-cell clones that produce IL-5 ongoing, um, and, uh, and, and we, we don' have a good sense of why this might be in most individuals. Perhaps trying a different anti-IL-5 therapy, one that blocks the receptor like benralizumab may have been more efficacious in that regard as well.

Dr. Panettieri:
Good, good point. Jonathan, any other comments?

Dr. Corren:
The only thing I would consider is whether or not it makes sense to go from one anti-eosinophilic drug to another. We know that with mepolizumab, on average, there's been about an 80% reduction in blood eosinophils, irrespective of wherever they start, and in similar findings have been found with the other anti-IL-5 drug, reslizumab. We know with benralizumab, which doesn't bind to IL-5 itself but binds to the receptor, causing apoptosis of the eosinophil, that it's, it's very common to find an eosinophil count of zero, um, following the institution of therapy. Um, at this point in time, there's not a lot of data suggesting that switching from an anti-IL-5 necessarily to going to an anti-IL-5 receptor drug will make a significant difference.

Dr. Panettieri:
Very good point. All good points. Um, so this is a challenging case, no doubt about it. Just to reiterate, I think the comorbidities that were raised really need to be addressed. In the, uh, patient that is unresponsive or not completely responsive to therapy, it's often because there's other mitigating circumstances. And, certainly, adherence needs to be considered, but I think we've hit all the major points here – uh, the use of macrolides as, uh, addressing a neutrophilic, uh, pathogenesis, uh, is, is important, um, and, and I agree wholeheartedly

with my colleagues in, uh, what needs to be the next approach. The switching of this within the anti-IL-5 category or class is intriguing with different mechanisms of action. And, again, we don't know about, uh, phenol in this case and whether maybe another biologic could have impact. I want to thank you both for the insight on this difficult case, and, hopefully, our physician colleagues and provider colleagues will have, uh, gained insight. I want to thank you for joining us today and don't forget, as you did with the pretest, to complete the posttest in this case. Thank you and have a wonderful day.

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