Transcript Details

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Understanding the Pathophysiology of Eosinophilic Asthma

Announcer:
You're listening to *Clinicians Roundtable* on ReachMD. On this episode, sponsored by GlaxoSmithKline, we'll hear from Dr. Praveen Akuthota, who's a pulmonary and critical care physician and Associate Professor of Medicine at UC San Diego Health. Dr. Akuthota is here to share his key insights on the pathophysiology of eosinophilic asthma. Let's hear from him now.

Dr. Akuthota:
So it's important to remember that eosinophils are part of a complex set of allergic mechanisms in eosinophilic asthma. So, eosinophils are not the only component or driver of disease. There are other allergic mechanisms involved. But that said, eosinophils themselves are indeed an important mechanistic component of driving disease and asthma. Eosinophils have been noted in the airways in asthma for a long time. From the turn of the 20th century, there have been autopsy studies that noted eosinophils in the airways in asthma to more classic studies later in the 20th century showing that airway biopsies correlated with eosinophil levels, and airway biopsies correlated with asthma severity. But it was really only in the last 20 years or so that we've understood that eosinophils indeed have mechanistic importance. Some of those data are from animal studies, but also some of that data is from the effect of using eosinophil-depleting therapy to patients with asthma. So, it's kind of been a proof of principle that eosinophils themselves are indeed important mechanistically. And eosinophils act by secreting cytotoxic granule products from their characteristic granules, which damage airway tissue. They also have complex immunoregulatory roles, which are sometimes underappreciated in how they interact with other immune cells in allergic inflammation. And the other components of that allergic inflammation are indeed important in eosinophilic asthma, including effects of cytokines like IL-4, IL-13, a new body of research over the last several years, which is now becoming manifested in therapies; the presence of alarmins, like IL-25, IL-33, and TSLP; the importance of IgE in eosinophilic asthma as well; and then, the importance of other immune cells, including Th2 lymphocytes, and mast cells to name a few.

The genetic and environmental factors that are involved in asthma are complex, but extremely important. I'll start with the genetic roles or genetic effects in asthma. I think many of us who are clinicians kind of intuitively know just from taking histories that patients with asthma often have relatives with asthma, other atopic disease, so there's clearly, at least from that perspective, a strong potential genetic associations with asthma. But when you go into the research, there is not one smoking gun; this is not a monogenic disease, where there's one individual genetic abnormality that confers a huge increased risk for asthma. But there are indeed many smaller effects from genetic polymorphisms, including many parts of allergic pathways. There's one gene locus in particular – the ORMDL3 locus – that has been implicated over and over again in conferring risk for asthma. These genetic risks, they interact in very complex ways with the environment. We know that the environment also is extremely important in conferring risk for asthma, both at a young age in the perinatal and infant period through childhood and into adulthood. That exposure to allergens, pollutants, and other irritants can increase the risk of developing asthma; children who grow up in environments that have increased cockroach allergen and other allergens have increased risk for asthma.

We also conversely know that potentially growing up in cleaner environments – the so-called "hygiene hypothesis" – may confer additional risks for asthma and may explain why, in the western world, we're seeing over the last few decades an increased risk of asthma. And then, also importantly, there's an entire branch of research called epigenetics, where the interaction of the environment on genes is studied, so we know that the environment causes genetic marks that affect the expression of particular genes and that epigenetic changes have profound impacts on asthma risk as well.

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