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The Neutrophil and Neutrophil Serine Proteases (NSPs) in Non-CF Bronchiectasis (NCFBE)

Announcer:
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Dr. Basavaraj:
Hi, my name is Ashwin Basavaraj. I'm Section Chief of Pulmonary Critical Care and Sleep Medicine at Bellevue Hospital Center in New York City, and Associate Director of our Bronchiectasis and NTM Program at NYU Langone Health. We're going to be talking about the neutrophil and neutrophil serine proteases in non-CF bronchiectasis.

So first, what is bronchiectasis? The way I like to explain it to my patients is that it's just an irreversible dilation of the airways. And there could be a number of reasons. There could be autoimmune conditions, there could be immunoglobulin deficiencies, genetic conditions, chronic infections. And what happens when these airways are dilated is that mucus can get stuck in these large airways, which then becomes difficult to remove. And then chronic infections and bacteria can take advantage of this, which leads to a cycle of repeated infections and inflammation.

These are some examples here of what we see on a CAT scan with bronchiectasis. On the top left, you have a normal airway. On the top right, you have what's known as cylindrical bronchiectasis, that looks like a cylinder. On the bottom right is more of a cystic form of bronchiectasis. And on the bottom left is a varicose bronchiectasis, it looks like varicose veins. Those are just different ways we describe bronchiectasis radiographically.

With bronchiectasis, it can present with nonspecific symptoms. You can have a chronic cough, fatigue, mucus production, weight loss, and oftentimes given the inflammation that occurs with bronchiectasis, this can lead to repeated flare-ups or exacerbations. And what is a bronchiectasis exacerbation? A bronchiectasis exacerbation is defined as a deterioration in 3 or more of the following symptoms:

Worsening cough, sputum volume, sputum purulence, shortness of breath, fatigue, coughing up blood, and a clinician determines that a change in bronchiectasis treatment is required. Normally, prescription of antibiotics. If a patient has worsening symptoms, 3 or more symptoms, and needs a change in treatment for at least 48 hours, that, by definition, is a bronchiectasis exacerbation.

And why is that important to determine? It's important to identify these bronchiectasis exacerbations because when exacerbations occur, they can have an effect on lung function, symptoms, quality of life, mortality, and it may lead to more recurrent future exacerbations. So it's important to try to identify these exacerbations early and treat it appropriately.

Now when we talk about bronchiectasis, classically we talk about the vicious cycle. And what is that? What that is, is that when bronchiectasis occurs, again, you have dilated airway that leads to abnormal mucus clearance, and then bacteria take advantage of that, and you can have repeated colonization, infections, and that can lead to further inflammation, oftentimes neutrophilic inflammation, and that leads to further bronchiectasis in this repeated cycle.

And treatment of bronchiectasis is often focused on disrupting this vicious cycle to try to prevent bronchiectasis from worsening. This

idea of the vicious cycle has morphed into the vicious vortex on the right here, where even if you try to stop one step in this vicious cycle, the bronchiectasis still may progress, and you need to focus on multiple steps of the cycle in order to try to prevent the bronchiectasis from worsening. So we try to identify causes of bronchiectasis and try to prevent that from getting worse. We try to help with mucus clearance. We treat chronic infections, oftentimes with inhaled antibiotics. And we do try to target inflammation, most commonly neutrophilic inflammation, to try to prevent the bronchiectasis from worsening.

And with neutrophilic inflammation, in bronchiectasis, neutrophils are often reprogrammed, which means that they're - that they have prolonged survival, they have delayed apoptosis, it can lead to impaired killing of organisms and impaired phagocytosis. Most commonly a deficient killing of some of the resistant organisms and bronchiectasis, like Pseudomonas. And what happens is that, with inflammation, it forms these neutrophilic extracellular traps, or NET formations, and that try - those NETs try to trap these organisms to really attempt to kill it. And oftentimes though, these NET formations, which are fibrin, mucus, you know, DNA that's degraded, becomes difficult to clear. And that by itself can lead to symptoms and worsening outcomes. So a lot of treatments now are trying to focus on reducing the NET formation to try to prevent worsening symptoms in bronchiectasis.

When we talk about mechanisms of antineutrophil inflammatory therapy in bronchiectasis, it's really targeting the diagram on the bottom left here, the neutrophils at the maturation state. For example, there's an enzyme called cathepsin C or dipeptidyl peptidase. And when that's activated, it can lead to serine proteases, neutrophil elastase, proteinase 3, cathepsin G, which is meant to try to treat infection but then oftentimes can lead to further inflammation and lung destruction. So these antiinflammatory therapies are trying to inhibit the release of these serine proteases to try to prevent the inflammation from worsening.

And there's a number of clinical trials studying antineutrophil therapy in bronchiectasis. These are some here that are highlighted. There are various forms of clinical trials in different phases currently.

So in summary, bronchiectasis can present with nonspecific symptoms, and it's often heterogeneous. Exacerbations are important to identify and treat appropriately, they lead to diminished quality of life and frequent symptoms, and can have an effect on mortality. Inflammation is a key component of the vicious vortex, and emerging therapies are trying to reduce the frequency of exacerbations and reduce inflammation to really try to prevent the bronchiectasis from worsening.

Thank you.

Announcer:
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