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CRSwNP: Exploring the Role of Nasal Epithelium and Epithelial Cytokines

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled “CRSwNP: Exploring the Role of Nasal Epithelium and Epithelial Cytokines,” is sponsored by Amgen and AstraZeneca. And now, here’s Dr Kathleen Buchheit and Dr Joseph Han.

Dr Buchheit:
Hi, I'm Dr Kathleen Buchheit. I'm an Assistant Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital, specializing in allergy and immunology, and I'm joined by my colleague Dr Joseph Han. Together, we'll be discussing chronic rhinosinusitis, or CRS, with a focus on chronic rhinosinusitis with nasal polyps, abbreviated as CRSwNP.

Although patients with chronic rhinosinusitis with nasal polyps make up about 20% of total chronic rhinosinusitis cases, patients with nasal polyps tend to have more severe clinical chronic rhinosinusitis disease and a poor quality of life.[1–3] So, with that in mind, I'm looking forward to our discussion today, Dr Han, as we take a closer look at our evolving understanding of the pathophysiology of chronic rhinosinusitis with nasal polyps.

Dr Han:
Yes, thanks Dr Buchheit.

Hi. I'm Dr Han, I'm Vice Chair, a Professor and Chief of Division of Allergy and used to be the Chief of the Division of Rhinology at Eastern Virginia Medical School. It's part of Old Dominion University in Norfolk, Virginia.

Now, often, patients with chronic sinusitis with nasal polyp will continue to have severe symptoms despite therapy. So, understanding the underlying inflammatory response and how epithelial dysfunction plays a role, may help inform clinical decision-making process,[4] so I'm glad to have this conversation with you today.

Dr Buchheit:
So, let's get started. Dr Han, could you give us an overview of chronic rhinosinusitis, especially focusing on chronic rhinosinusitis with nasal polyps?

Dr Han:
Certainly. Chronic rhinosinusitis is characterized with at least 12 weeks of persistent symptoms, one of the symptoms being either nasal discharge or nasal obstruction. Sometimes nasal obstruction is synonymous with nasal blockage or congestion. Patients may also have facial pressure or pain, as well as reduction and loss of sense of smell.[5] Among these symptoms, nasal congestion and loss of smell are particularly troublesome for our patients with sinusitus.[2,6]

Now looking specifically at CRSwNP, it’s estimated to affect 1.1 percent of the U.S. population and is associated with a low quality of life as well as increased healthcare utilization.[1,7] And unfortunately, the mean time from the first symptom to diagnosis is 1.5 years in the U.S.[8] Some of the challenge in making the diagnosis includes routine nasal endoscopy to assess nasal polyps.[9,10]

So with that background in mind, Dr Buchheit, can you speak on the burden of disease and some of the challenges in managing CRSwNP?

Dr Buchheit:
Yes, and as you mentioned a few minutes ago, patients with CRSwNP have significantly higher healthcare utilization compared to those

without CRS and they also have twice as many doctor's office visits, approximately one-and-a-half times more emergency department visits, and two-and-a-half times higher incremental healthcare costs as CRSwNP incurs an annual cost of almost $20,000 per patient on average.[11]

And despite optimized medical therapy and surgical intervention, approximately 40 percent of patients remain uncontrolled.[4] In fact, intranasal steroids are prescribed in over 90 percent of patients who have CRSwNP, but they often fail to provide long-term control.[2,12,13] And oral corticosteroids are prescribed in up to 71 percent of patients for short-term management, but serious side effects limit their long-term use and resistance has been reported.[12,14–16]

So unfortunately, many patients experience nasal polyp recurrence despite optimized medical therapy and surgery, and this is potentially due to unaddressed underlying inflammation.[17,18] For example, within three to five years after surgery for CRSwNP, about 80 percent of patients report inadequately controlled symptoms.[4] And for those with recurrent nasal polyps, the interval between surgeries tends to shorten as the number of revision surgeries increases.[19]

Now that we have this context, I'd like to switch gears a bit here and focus on the underlying pathophysiology of CRSwNP. Dr Han, could you tell us about our current understanding of the pathways that lead to nasal polyps and CRS symptoms?

Dr Han:
Sure, so CRSwNP actually involves heterogeneous inflammatory endotypes which often overlap.[20–23] Type one inflammation involves the release of IFN-γ that is produced by Th1 cells, cytotoxic T cells, natural killer cells, and ILC1 cells, and it typically presents with headache and facial pain.[20,21] Type two inflammation, on the other hand, results from IL-4, IL-5, and IL-13 produced by Th2 cells, mast cells, ILC2 cells, and basophils.[21] It is characterized with a loss of smell and asthma comorbidity.[20–22] There is also type three inflammation, which involves IL-17 and IL-22 from Th17 cells and ILC3 cells, and it presents with purulent rhinorrhea.[20–22]

Now it's important to note that many patients with CRSwNP have a mixed endotype, and about nine percent of patients have no clear endotype. And they can also vary geographically.[20–22] In the Western countries, the majority of patients exhibit type two inflammatory endotype.[20,21]

Dr Buchheit:
Got it. So, these endotypes provide a helpful framework for understanding the inflammatory pathways in CRSwNP, but now let's dive a little deeper into what's happening at the epithelial level. Could you discuss how the nasal epithelium is affected in CRSwNP?

Dr Han:
Well, to start off, we're learning that the nasal epithelium plays a crucial role in CRSwNP. In the healthy state, it acts as a barrier, supports mucociliary clearance, and is actively involved in innate and adaptive immune responses.[24] But in CRSwNP, the nasal epithelium is significantly altered with increased permeability, excess mucus production, and impaired mucociliary clearance.[1,25–28]

We also see infiltration of the eosinophils, thickening of the basement membrane, and epithelial sloughing.[29]

With the impaired physical and immune barrier, pathogens and environmental insults further promote epithelial injury and induces epithelial cytokine release, which then activates immune cells and downstream mediators and amplifies the inflammatory immune response.[1,5,21]

So, Dr Buchheit, can you talk more about the role of epithelial cytokines such as TSLP, IL-25, and IL-33, and how do they contribute to the inflammation in CRSwNP?

Dr Buchheit:
Yeah, certainly. So, in patients with type two inflammation, triggers such as bacteria, viruses, and pollution can interact with the defective—and more easily permeable—epithelium to cause release of TSLP, IL-25, and IL-33. Then through multiple pathways, including the activation of innate type two lymphoid cells and mast cells, these epithelial cytokines can lead to production of downstream mediators such as IL-4, IL-5, and IL-13, which further amplify the T2 inflammatory response.[5,21,30]

Subsequently, IL-5 activates eosinophils, while IL-4 and IL-13 activate epithelial cells, endothelial cells, macrophages, and B cells to induce barrier dysfunction, mucus response, and IgE-mediated responses.[25]

And studies show that the epithelial cytokines TSLP, IL-25, and IL-33 are significantly increased in the nasal mucosal epithelial tissue of patients with eosinophilic CRSwNP, which is commonly associated with type two inflammation.[31]

In these patients, the levels of TSLP, TSLP receptor, and IL-33 receptor mRNA expression in nasal polyp tissue and nasal epithelial cells also have been found to correlate with disease severity, as measured by CRSwNP symptoms and sinus opacification on CT scans, as well as with type two inflammation, as measured by increases in IL-5, IL-13, and eosinophils.[32]

But despite the evident association with type two inflammation, we also see some increase in these epithelial cytokines in patients with non-eosinophilic CRSwNP, suggesting a potential role for epithelial cytokines in other, non-type-two inflammatory endotypes.[31]

So it's fascinating how epithelial cytokines interact with the immune cells to drive inflammation. Dr Han, building on this, could you discuss how epithelium dysfunction and epithelial cytokines contribute to the nasal polyp formation?

Dr Han:
Sure. So for nasal polyp formation, the epithelium is once again key here as the epithelial cells drive this process through the following steps:

First, the epithelial damage triggers the proliferation and transition of epithelial cells to mesenchymal cells, which are capable of altering inflammatory and remodeling processes.[33,34]

Next, the release of the epithelial cytokines or “alarmins” such as TSLP and IL-33 drive activation of multiple downstream pathways involved in the disease pathogenesis including activation of mast cells as well as production of other downstream cytokines such as IL-4, IL-5, and IL-13.[25]

These activated mast cells, along with basophils, promote edema in the mucosa, which causes the nasal blood vessels to leak plasma.[25]

As a result the activation of the coagulation pathway, the cross-linked fibrin accumulates and forms a dense mesh, which traps plasma proteins and promotes further edema.[25,35]

And finally, IL-4 and IL-13 also suppresses the tissue plasminogen activator, reducing its ability to break down the fibrin mesh.[25,36]

ReachMD Announcer:
For those just tuning in, you’re listening to ReachMD. Today, Dr Joseph Han and Dr Kathleen Buchheit are sharing insights on the underlying pathways in CRSwNP and the important role of the nasal epithelium in the disease.

Dr Han:
So, now that we've reviewed the pathway that leads to nasal polyps and chronic sinusitis symptoms, I'd like to come back to something we discussed earlier.

Dr. Buchheit, you mentioned earlier how olfactory dysfunction has an important effect on our patient’s quality of life. So, how does the inflammation affect the sense of smell?

Dr Buchheit:
Yes, so this is such an important question because unfortunately, CRS has significant impacts on health-related quality of life as it comes with substantial psychological and social burden by reducing enjoyment in food, sleep quality, and ability to perform daily activities.[2,6]

Olfactory dysfunction is a key predictor of reduced quality of life and is associated with increased anxiety, phobia, and depression scores.[2,37]

Now if we look at how a patient’s sense of smell can be impacted, both chronic inflammation and local inflammation play a role in contributing to dysfunction and death of olfactory neurons.[38–41] And because physical obstruction of the nasal cavities and tissue edema from chronic inflammation can reduce the airflow to the olfactory epithelium, olfactory dysfunction is more prevalent and more severe in patients with CRS who have nasal polyps versus those without them.[39,42–45] And unfortunately, endoscopic sinus surgery and steroid treatment typically provide only temporary relief for these patients.[17,38]

Dr Han:
Dr Buchheit, you know, we often hear about the connection between the upper and lower airway diseases. How does CRSwNP relate to the lower airway disease like asthma, and what does it mean for the management of patients with these overlapping respiratory issues?

Dr Buchheit:
Yes, this is a great question. There is a bidirectional relationship between upper and lower airway diseases. For example, patients with

CRSwNP often have coexisting asthma and other inflammatory conditions like aspirin-exacerbated respiratory disease, which we refer to as AERD for short.[46,47] And this coexistence suggests a common underlying pathophysiology, which has led to the concept of the unified airway disease.[47]

For example, up to 67 percent of patients with CRSwNP also have asthma.[1] And, these patients tend to experience a greater disease burden and reduced quality of life compared to patients with CRSwNP who do not have asthma.[1,9] Also, asthma in the presence of nasal polyps is generally more difficult to control.[1,48]

Now AERD is a sub-phenotype of CRSwNP, which should be distinguished during diagnosis. It's prevalent in about 30 percent of patients with both asthma and CRSwNP and it's characterized by asthma, rhinosinusitis with nasal polyps, and acute respiratory reactions to aspirin or NSAIDs.[49,50]

So given the close relationship between CRSwNP with asthma and AERD, it's clear that managing these conditions requires a comprehensive approach.

Now, as we near the end of our program today, Dr Han, I'd be interested in your perspective on working with other providers like allergists and primary care providers to manage patients with nasal polyps.

Dr Han:
Yeah, I think that's a very important question. And I think, you know, when we see patients with chronic sinusitis with nasal polyps, I believe it's a systemic disease, and I think it's important to have a multidisciplinary team approach. What do you think, Dr Buchheit?

Dr Buchheit:
Yeah, I agree. We work closely with the rhinologists at our institution as well as the pulmonologists to manage comorbidities and also facilitate the timing of both surgical and medical management.

And with those thoughts in mind, I'd like to thank Dr Han for sharing his insights on the pathophysiology of chronic rhinosinusitis with nasal polyps. Dr Han, it was great speaking with you today.

Dr Han:
You as well. And I'd like to thank you, Dr Buchheit, for sharing your wonderful clinical experience managing chronic sinusitis with nasal polyp. Dr Buchheit, it's been a pleasure. Thank you.

ReachMD Announcer:
This medical industry feature was sponsored by Amgen and AstraZeneca. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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