Biology of nasal polyposis

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CLINICAL VIGNETTE

A 38-year-old woman with a history of allergic rhinitis and asthma presented for evaluation of nasal congestion, rhinorrhea, postnasal drip, and sneezing. Although her asthma had remained well controlled with inhaled corticosteroids for many years, her nasal symptoms had been steadily worsening for at least the past 12 months. During her clinical visit, spirometric results were within normal limits, and aeroallergen skin test results were positive for tree, ragweed, grass, dust mite, and cat. On examination, her nasal turbinates were moderately edematous, but no nasal polyps were visualized. A sinus computed tomographic scan revealed only mild sinus disease. She was treated with a short course of oral steroids, antibiotics, and nasal steroids, as well as educated on allergen avoidance. Her nasal symptoms were manageable for 4 years with intranasal steroid therapy alone.

At age 43 years, she began to experience recurrent episodes of worsening nasal congestion, facial pressure, headaches, and hyposmia, each associated with an asthma exacerbation. She was prescribed courses of oral steroids and antibiotics, with only temporary relief of symptoms. A repeat sinus computed tomographic scan at this time showed pansinusitis consistent with chronic rhinosinusitis (CRS), and nasal endoscopy revealed frank polyps (see Fig E1 in this article's Online Repository at www.jacionline.org). Additionally, the patient recalled recently taking ibuprofen for a headache and experiencing acute shortness of breath and worsening of nasal congestion within 30 minutes of ingestion. Before this episode, she had tolerated aspirin and ibuprofen without problems. Because the patient demonstrated the clinical triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and sensitivity to a nonsteroidal anti-inflammatory drug, she was given a diagnosis of aspirin-exacerbated respiratory disease (AERD)[E1] and instructed to avoid all nonsteroidal anti-inflammatory drugs.

The full review of this article, including a preview of relevant issues to be considered, can be found online at www.jacionline.org. *If you wish to receive CME or MOC credit for the article, please see the instructions above.*

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REVIEW

Nasal polyps are inflammatory outgrowths of the paranasal sinus mucosa and occur in 1% to 4% of the general population.[E2] They develop in the setting of chronic mucosal inflammation of the sinuses and can include subgroups of AERD and allergic fungal rhinosinusitis. Nasal polyps most often are benign, occur bilaterally, and typically develop in adulthood. Unilateral nasal polyps should be evaluated for malignancy,[E3] and nasal polyps found in children should raise the suspicion for underlying cystic fibrosis.[E4]

Several theories regarding the development and pathogenesis of nasal polyposis have been proposed. The following is an overview of factors relevant to the biology of nasal polyposis, with a focus on the roles of barrier function, innate immunity, eosinophilic inflammation, and adaptive immunity.

Role of barrier function and innate immunity

The sinus mucosa forms an important barrier protecting the host from constant exposure to foreign antigens. Compromise of this barrier has been hypothesized to cause dysregulation of local immune homeostasis and lead to a chronic inflammatory state.[E5] There have been several studies examining sinus mucosal function and integrity in patients with CRS. Levels of S100A7 and S100A8/9, proteins important in epithelial defense and repair, were reduced in nasal lavage fluid from patients with CRSwNP compared with levels seen in healthy control subjects.[E6] Additionally, RNA levels of the serine peptidase inhibitor Kazal type 5 *(SPINK5)* were reduced in epithelial scrapings from sinonasal tissues from patients with CRSwNP compared with those seen in healthy control subjects.[E7] Furthermore, Soyka et al[E8] showed that expression of the tight junction proteins occludin and zonula occludens 1 are decreased in nasal polyps also when compared with expression seen in healthy control subjects. Taken together, there appears to be impairment of tight junctions and decreases in various proteins important in epithelial defense, suggesting that the mucosal barrier in patients with CRSwNP is compromised. Similar barrier integrity loss has been reported in patients with atopic dermatitis and asthma.[E9,E10] Disruption in barrier integrity generally increases allergic sensitization and could increase epithelial susceptibility to colonization by fungal or bacterial pathogens, allowing access to proteases and allergens that could drive the chronic inflammation characteristic of nasal polyposis.

Eosinophilia and CRS

Studies from the United States and Europe have shown that nasal polyps are characterized by predominantly eosinophilic inflammation.[E11] Levels of soluble mediators important in eosinophil activation, proliferation, recruitment, and survival have been shown to be increased in nasal polyp tissue from patients with CRS compared with those in healthy control subjects.[E11,E12] Additionally, patients with AERD have even greater levels of nasal polyp eosinophilia than those with CRSwNP alone.[E13] The significance of tissue eosinophilia and whether eosinophils have a causative versus bystander role in the development of nasal polyps remain unclear and are subjects of active investigation.[E14]

As opposed to Western countries, subjects living in Asia are less likely to have a predominant eosinophilic infiltrate in nasal polyp tissue. Instead, a predominantly neutrophilic infiltrate has been more commonly reported in Thai, Chinese, Korean, and Japanese cohorts.[E15] It can be hypothesized that differences in CRSwNP among patients living in Eastern versus Western countries might be due to possible genetic factors, environmental factors, or both. Interestingly, a recent study examining cohorts in Korea found a shift from neutrophil- to eosinophil-predominant cases of CRSwNP in a 17-year period, leading the authors to suggest that the specific factors important in CRSwNP pathogenesis might be evolving and are modifiable.[E16]

Mast cells have also been studied in patients with CRS because of their ability to not only recruit eosinophils and basophils but also produce mediators that can induce vasodilation and tissue edema, findings observed in nasal polyps. Takabayashi et al[E17] found increased numbers of mast cells in nasal polyps when compared with nonpolypoid CRS tissue and tissue from healthy control subjects. Additionally, mast cells within nasal polyp epithelium were shown to express tryptase and carboxypeptidase A3, but not chymase, an unexpected finding given mast cells are traditionally classified as either expressing all 3 proteases or just tryptase alone.[E17,E18] Taken together, the increased presence and phenotypic differences of mast cells in nasal polyp tissue suggest these cells might play a role in sinus disease pathogenesis.

Numbers of basophils, which are often companion cells to eosinophils, were recently shown to be increased in nasal polyps.[E19] Interestingly, however, basophil numbers are lower in nasal polyps of patients with AERD compared with numbers in those with CRSwNP alone, and it has been suggested that this might reflect degranulation of those basophils that appear in nasal polyps from patients with AERD.[E19]

Role of adaptive immunity

B lymphocytes are integral components of the adaptive immune response, during which they can produce immunoglobulins, secrete various cytokines, and present antigen to T lymphocytes. Studies have shown that activated B cells are more numerous in nasal polyps.[E20] Increased levels of B cells in nasal polyps might in part be secondary to increased expression of CXCL12 or CXCL13, which are B cell–attracting chemokines, or caused by increases in a key B-cell survival factor, B cell–activating factor of the TNF family, which is found in polyp tissue.[E5] There is evidence to suggest that B cells also differentiate vigorously within nasal tissue to become plasma cells that produce immunoglobulins, and levels of total IgG, IgE, and IgA in nasal polyp tissue are increased compared with those seen in healthy control subjects.[E21] Importantly, in this study there were no corresponding differences in circulating levels of total IgG, IgA, or IgE between subjects with CRSwNP and control subjects. It is possible that local immunoglobulin production occurs for the purpose of host defense in patients with CRSwNP because of frequent colonization, infection, or both. It is also being considered that local immunoglobulin production might mediate pathogenesis in nasal polyps, and local synthesis of autoantibodies has been documented and hypothesized to be of potential pathogenic importance.[E22] Whether

protective or pathogenic, it is becoming clear that there is a robust local B lineage cell response and production of immunoglobulins.

There is evidence to suggest that many patients with CRSwNP are colonized with *Staphylococcus aureus* and can have a polyclonal population of IgE antibodies both locally[E23] and systemically.[E24] In a subset of colonized patients, specific IgE to *S aureus* enterotoxins can develop, and these levels directly correlate to the amount of detectable IL-5 and eosinophil cationic protein, as well as to the number of eosinophils present in polyp tissue.[E25] The presence of such enterotoxins also influences local T-cell diversity because T lymphocytes in nasal polyp tissue undergo a more significant T-cell receptor V-β expansion compared with those T lymphocytes in circulation.[E26] Additionally, polyclonal IgE was shown to activate mast cells *ex vivo* in patients with allergic rhinitis and nasal polyposis, and it is hypothesized that specific IgE to *S aureus* enterotoxins functions similarly *in vivo*.[E27]

T lymphocytes are very important in the adaptive immune response and have been shown to play an important role in CRS pathogenesis. CD4 T-cell numbers are increased in nasal polyp tissue and appear to be skewed toward a T_H2-type phenotype.[E28] Thymic stromal lymphopoietin, which is known as the master regulator of T_H2 inflammation, is produced by immune cells and epithelial cells and activates dendritic cells to promote a T_H2 response.[E29] Nagarkar et al[E30] have shown that thymic stromal lymphopoietin expression not only is increased in epithelial scrapings from nasal polyps in patients with CRS but also is linked with T_H2 inflammation, as evidenced by a positive correlation with IL-5 expression in polyp tissue. Although T_H2 cells have been identified in nasal polyps, recent studies indicate that a cell type of potentially more importance is the type 2 innate lymphoid cell.[E31] These cells generally drive a T_H2-type inflammation that is antigen independent and in which IL-5 and IL-13, but not IL-4, are the predominant cytokines. Finally, $CD4^+$ regulatory T-cell function in patients with CRSwNP might be impaired because studies have shown that forkhead box protein 3 *(FOXP3)* mRNA expression and TGF-β protein levels are both decreased in nasal polyp tissue compared with those seen in control tissue.[E28] This possible imbalance between effector and regulatory T-cell function could thus contribute to the chronicity of the ongoing inflammatory response in nasal polyposis.

Nasal polyps and tissue edema

In addition to an inflammatory cell infiltrate, nasal polyps are also characterized by edematous stromal tissue and the formation of pseudocysts. The retention of plasma proteins, such as albumin, has been suggested to contribute to polyp size and growth,[E32] but the precise mechanisms underlying how such proteins are retained remains unclear. However, recent studies have suggested that products of the coagulation cascade might be important in the development of tissue edema observed in patients with CRS.

Levels of fibrin, a key protein involved in clot formation, were found to be increased in nasal polyp tissue, whereas levels of D-dimer, a measure of fibrin breakdown, and tissue plasminogen activator, a protein involved in fibrin degradation, were both reduced.[E33] Additionally, levels of an initiator of the coagulation cascade, Factor XIII-A, are also increased in nasal polyp tissue. Factor XIII-A is predominantly produced by M2 macrophages, a subset of macrophages alternatively induced by T_H2 cytokines that play a

role in tissue repair and fibrosis.[E34] Taken together, it is hypothesized that the T_H2 environment seen in patients with CRSwNP recruits M2 macrophages, which in turn secrete Factor XIII-A and promote fibrin deposition. The same T_H2 environment also is thought to attenuate tissue plasminogen activator and decrease the rate of fibrin degradation. Such imbalance in the generation versus breakdown of fibrin could lead to an enhanced fibrin deposition that could retain plasma proteins and contribute to nasal polyp edema.

Nasal polyps in patients with AERD

On average, patients with AERD have significantly more extensive sinus inflammation and higher recurrences of nasal polyps after surgery when compared with patients with CRSwNP alone.[E35] The biological mechanisms that account for these clinical differences are currently under investigation, with the dysregulation of arachidonic acid metabolism hypothesized to play an important role.[E36,E37] Studies have shown reduced levels of prostaglandin E_2, an anti-inflammatory lipid mediator, and decreased mRNA levels of COX2, a key enzyme that synthesizes prostaglandin E_2, in nasal polyp tissue from patients with AERD compared with patients with CRSwNP alone.[E12,E38,E39] In contrast, levels of proinflammatory cysteinyl leukotrienes and mRNA expression of their receptors, cysteinyl leukotriene receptors 1 and 2, were found to be increased in nasal polyps from patients with AERD compared with those from patients with CRSwNP.[E12,E40] A recent study by Laidlaw et al[E41] reported increased numbers of platelets colocalizing with leukocytes in nasal polyp tissue from patients with AERD compared with those with CRSwNP, and these authors suggest that such adherent platelets might enhance tissue inflammation in patients with AERD in part by contributing to leukocyte adhesion and production of cysteinyl leukotrienes.

THE CASE REVISITED

The patient underwent sinus surgery but had postoperative recurrence of symptoms requiring a second revision surgery 15 months later. Although sinus surgery is the most aggressive treatment modality to address nasal polyps, concomitant medical therapies are also important in the management of this disease. Most commonly, nasal steroids are prescribed based on evidence showing their ability to reduce polyp size, improve sinonasal symptoms, and positively affect quality of life.[E42,E43] More recently, a randomized, double-blind, placebo-controlled trial examined the effects of omalizumab, an mAb that binds IgE, in patients with CRSwNP and comorbid asthma.[E44] This study found a significant decrease in total nasal endoscopic polyp scores, as well as improvement in nasal symptoms, in the treatment group compared with values in placebo-treated control subjects. The exact mechanisms behind these observations are not known, but one hypothesis is that omalizumab reduces the levels of localized polyclonal IgE in nasal polyp tissue, thus limiting the ability of IgE to activate innate and adaptive immune responses. Interestingly, the treatment was effective in both atopic and nonatopic patients with CRS, suggesting that the mechanism might be more complex. After nasal steroids and surgery, omalizumab was initiated in the present patient, with significant improvement in both her clinical symptoms and endoscopic findings. Aspirin desensitization and subsequent treatment with high doses of aspirin were discussed with the patient because this therapy has been shown to improve

sinus and asthma symptoms, as well as reduce the number of revision surgeries.[E45] However, the patient declined this treatment.

In conclusion, the biology of nasal polyposis represents a complex interplay between the sinonasal epithelial barrier and the host immune response, which together promote chronic inflammation that is characteristic of CRSwNP. It can be hypothesized that treatments that eliminate the recruitment and/or activation of eosinophils, mast cells, and lymphoid cells producing type 2 cytokines are expected to have beneficial effects in patients with CRSwNP.

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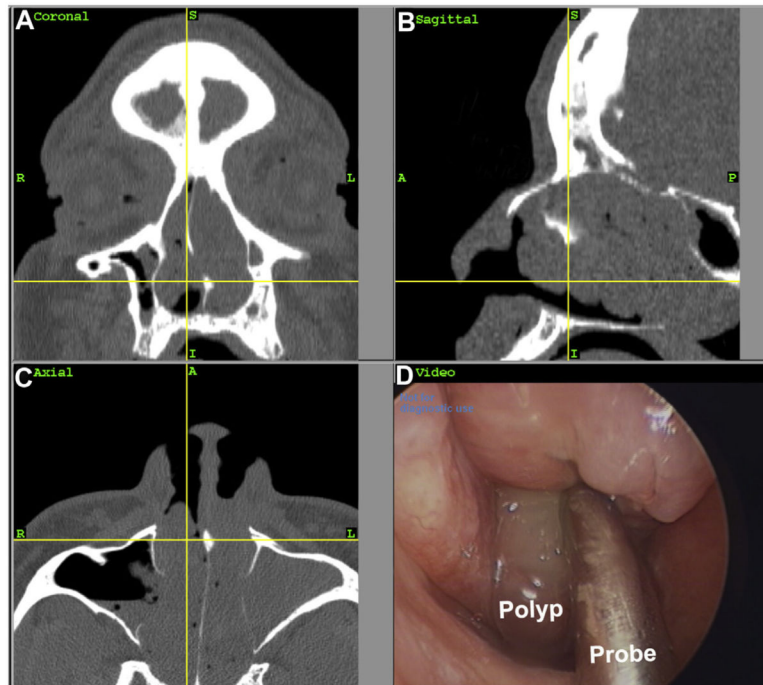
FIG E1.
Sinus computed tomography scan demonstrating mucosal thickening in coronal **(A)**, sagittal **(B)**, and axial **(C)** sections. Nasal endoscopy reveals the presence of a polyp **(D)**.