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Chronic Rhinosinusitis with Nasal Polyps

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an important clinical entity diagnosed by the presence of both subjective and objective evidence of chronic sinonasal inflammation. Symptoms include anterior or posterior rhinorrhea, nasal congestion, hyposmia and/or facial pressure or pain that last for greater than 12 weeks duration. Nasal polyps are inflammatory lesions that project into the nasal airway, are typically bilateral, and originate from the ethmoid sinus. Males are more likely to be affected than females but no specific genetic or environmental factors have been strongly linked to the development of this disorder to date. CRSwNP is frequently associated with asthma and allergic rhinitis but the cellular and molecular mechanisms that contribute to the clinical symptoms are not fully understood. Defects in the sinonasal epithelial cell barrier, increased exposure to pathogenic and colonized bacteria, and dysregulation of the host immune system are all thought to play prominent roles in disease pathogenesis. Additional studies are needed to further explore the clinical and pathophysiological features of CRSwNP so that biomarkers can be identified and novel advances can be made to improve the treatment and management of this disease.

Keywords

Chronic rhinosinusitis with nasal polyps; Nasal polyp; Chronic rhinosinusitis

Introduction

Nasal polyps are inflammatory outgrowths of sinonasal tissue that are estimated to occur in 1–4% of the US general population [1]. While nasal polyps are observed in a variety of clinical conditions including cystic fibrosis and malignancy, they are more frequently associated with a subset of chronic rhinosinusitis aptly named chronic rhinosinusitis with

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nasal polyps (CRSwNP). In this condition, nasal polyps are benign and typically develop bilaterally in the sinonasal cavity. Among all patients with chronic rhinosinusitis (CRS), only ~25–30% have CRSwNP. However, CRSwNP is associated with significant morbidity and decreased quality of life making this disease clinically important to identify, evaluate, and treat.

Demographics

CRSwNP is a disease of middle age with the average age of onset being 42 years and the typical age of diagnosis ranging from 40–60 years [1, 2]. Most commonly, nasal polyps present as bilateral inflammatory lesions originating in the ethmoid sinuses and projecting into the nasal airway beneath the middle turbinate. In contrast, isolated nasal lesions that present medial to the middle turbinate are concerning for neoplasm. Presumptive nasal polyps found in patients less than 20 years or greater than 80 years also raise suspicion for other clinical conditions. In children, cystic fibrosis becomes a concern [34] and unilateral nasal growths suggest a possible encephalocele. In adults, new onset polyps at an advanced age or in atypical locations suggest the possibility of neoplasm.

Males are more likely to have CRSwNP than females [1]. However, a 2015 study by Stevens and colleagues examining CRSwNP patients undergoing sinus surgery at a tertiary care center found that females with CRSwNP had more severe disease than males [5]. In this study, CRSwNP was diagnosed in 38% and 62% of females and males respectively. When compared to males, females had significantly enhanced radiographic evidence of sinus disease, were more likely to be taking systemic corticosteroids at the time of sinus surgery, and more often required revision sinus surgeries [5]. Additional studies are needed to better understand the underlying pathophysiological and societal factors that could be contributing to these observations.

Clinical Characteristics

By definition, patients with CRSwNP must report the presence of anterior or posterior rhinorrhea, nasal congestion, hyposmia and/or facial pressure or pain lasting for greater than 12 weeks duration [1]. However, these subjective findings are neither sensitive nor specific for CRSwNP alone and are used to also characterize patients who have chronic rhinosinusitis without nasal polyps (CRSsNP) [1]. On average, CRSwNP patients are thought to have more severe sinonasal symptoms than CRSsNP patients [6, 7].

To improve the ability to clinically distinguish CRSwNP from CRSsNP, several studies have compared symptom profiles of affected patients as a means to identify possible clinical factors unique to each condition. In a cohort of 126 CRS patients, Banjeri and colleagues found that nasal obstruction and hyposmia/anosmia were more significantly associated with CRSwNP while facial pain/pressure was more prevalent in CRSsNP patients [8]. Additional studies of CRS patients at separate tertiary care centers found CRSwNP patients were more likely to report rhinorrhea, severe nasal congestion and loss of smell/taste than patients with CRSsNP [9, 10]. However, in both studies, there was still a considerable overlap in symptoms

reported by both CRSsNP and CRSwNP patients, thus emphasizing the need for additional criteria to diagnose CRSwNP.

In addition to subjective assessments of CRSwNP, there must be objective evidence of sinonasal inflammation and nasal polyps on sinus CT scan and/or nasal endoscopy (Figure 1). Patients with CRSwNP on average have more extensive sinus disease than CRSsNP patients as measured by worse sinus CT and endoscopic scores[1178]. Even following sinus surgery, patients with CRSwNP can continue to have more severe objective measures of sinus disease than CRSsNP patients who also underwent surgery [6, 12]. It is thus not surprising that patients with CRSwNP on average are more likely to require revision sinus surgeries than CRSsNP patients [6].

Comorbidities

CRSwNP is often associated with other important medical conditions that can influence disease severity. In a large retrospective study evaluating over 400,000 primary care patients, those diagnosed with CRSwNP had a significantly higher premorbid prevalence of acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea [13]. How these conditions could contribute to the development of CRSwNP remains unclear.

The role of atopy in CRSwNP has been the focus of numerous studies. While the percent of allergic rhinitis patients with nasal polyps is similar to that of the general population (0.5–4.5%) [1], 51–86% of CRSwNP patients are sensitized to at least one aeroallergen [1114]. No study to date has established a relationship between sensitization by one particular aeroallergen and the development of CRSwNP, but sinus disease can worsen during allergen season [15].

Further complicating the understanding of CRSwNP are conflicting reports regarding the relationship between atopy and sinus disease severity. Some studies report that sinus CT and endoscopic scores are significantly worse in patients sensitized to inhalant allergens [11, 16] while other studies found no difference in sinus severity in sensitized and non atopic patients [14, 1715]. In summary, future investigations are needed to better explore how atopy may contribute to CRSwNP.

The association between asthma and CRSwNP has been more extensively defined. A large majority of asthmatics (~88%) have at least some radiographic evidence of sinonasal inflammation [1]. More specifically, CRSwNP is estimated to occur in 7% of all asthmatics while asthma is reported in 26–48% of patients with CRSwNP [1, 18]. Pearlman and colleagues found the prevalence of nasal polyps to be significantly greater in asthmatics compared to non-asthmatics within a tertiary care population[15]. Additionally, CRSwNP patients were more likely to have asthma than patients with CRSsNP, odds ratio of 7.5 [1911]. Increased asthma severity has also been shown to be associated with enhanced sinonasal inflammation [20].

There is a subset of patients with CRSwNP and asthma who also develop upper and/or lower respiratory tract symptoms following the ingestion of medications that inhibit the

cycloygenase-1 (COX-1) enzyme. Such patients have Aspirin Exacerbated Respiratory Disease (AERD). It is estimated that ~10% of patients with nasal polyps and 9% of patients with CRS have AERD [21] but the true prevalence of this disease remains unknown. Furthermore, AERD patients on average have more severe sinus disease and undergo more sinus surgeries than patients with CRSwNP alone [22]. There have been several important studies characterizing the clinical profiles of patients with AERD as well as defining unique underlying mechanisms in disease pathology [23, 24]. As such, AERD will not be further discussed in this review.

Pathophysiology

The underlying mechanisms that contribute to the chronic sinonasal inflammation observed in CRSwNP are not completely defined. Various research groups have focused on exploring the role sinonasal epithelial cells, the host immune system, and pathogens may play in CRSwNP pathogenesis (Figure 2). It is hypothesized that an impaired sinonasal epithelial barrier could lead to increased exposures to inhaled pathogens, antigens and particulates that, in the setting of a dysregulated host immune response, could promote chronic inflammation.

In healthy conditions, the epithelial cells which line the sinonasal mucosa not only form a physical barrier to protect the host from inhaled respiratory pathogens and particulates but also play critical roles in mucociliary clearance and host defense. In CRSwNP, the sinonasal epithelial barrier is defective leading to increased tissue permeability, decreased epithelial resistance, acanthosis, and acantholysis. Why the epithelial barrier is defective in CRSwNP remains unclear. It may be that epithelial cells are inherently abnormal in CRSwNP [25]. Alternatively, extrinsic factors unique to CRSwNP could impair an otherwise intact epithelial barrier and induce the breakdown observed in CRSwNP. To this end, Pothoven and colleagues noted that oncostatin M, a IL-6 family member, was elevated in CRSwNP nasal polyps and could induce tissue permeability, disrupt tight junctions, and decrease electrical resistance in cultured human epithelial cells [26].

Other aspects of epithelial host defense are also impaired in CRSwNP. For example, levels of epithelial-derived antimicrobial proteins including lysozyme, S100A7, S100A8/9, beta-defensins, and Palate, Lung, and Nasal Epithelial Clone (PLUNC) proteins were reduced in CRSwNP patients compared to healthy controls [2728–30]. Pendrin, an epithelial ion transporter that can increase mucus production, and Muc5AC, a type of mucin, were elevated in CRSwNP versus controls [3132]. These findings suggest that impairment in mucociliary clearance, reduction in antimicrobial defense protein secretion, and breakdown in the physical barrier can lead to chronic exposure of pathogenic and non-pathogenic mediators and the development of a chronic inflammatory response.

The dysregulation of the host immune system has also been extensively evaluated in CRSwNP. Originally, this disease was categorized by a type-2 inflammatory response with enhanced tissue eosinophilia. Levels of eosinophilic granule proteins (*e.g.* eosinophil cationic protein (ECP)), the eosinophilic survival factor (IL-5), and eosinophil chemotactic proteins (*e.g.* Eotaxin-1, Eotaxin-2, Eotaxin-3, MCP-4) are all elevated in CRSwNP nasal

polyps compared to healthy controls [33–38]. Studies have also reported CRSwNP to have increased numbers of basophils [39], innate type-2 lymphoid cells [40] and mast cells [41]. Additionally, type-2 cytokines including IL-5 and IL-13 [36] as well as the epithelial cell-derived thymic stromal lymphopoietin (TSLP)[42] are elevated in CRSwNP. While the inflammatory environment in CRSwNP has been extensively characterized, the specific events and signals that initiate this response are not well defined.

Further complicating the study of CRSwNP pathogenesis is the observation that not all nasal polyps have the same histological appearance. The original studies of type-2 inflammation and nasal polyps were completed in CRSwNP patients of European descent. However, a paper published in 2008 indicated that nasal polyps of Asian patients living in Asia lack enhanced tissue eosinophilia, have lower levels of IL-5, and increased levels of the type-1 cytokine IFN-γ when compared to nasal polyps from European patients [43]. As a result, genetic factors may also be contributing to CRSwNP pathology as discussed below.

In addition to innate immune response, the host adaptive immune system is also dysregulated in CRSwNP. Naive B cells and activated plasma cells are elevated in nasal polyps compared to healthy controls [44–46]. This is most likely in response to nasal polyps also having increased levels of CXCL-12 and CXCL-13 (factors important for B cell chemotaxis) as well as BAFF and IL-6 (factors that induce B cell proliferation and activation) [46, 4748]. Levels of IgG1, IgG2, IgG4, IgA, IgE and IgM are increased in nasal polyps but not in the circulation of patients with CRSwNP suggesting that local factors within the nasal polyp can activate B cells [45]. The exact specificity of the antibodies detected in CRSwNP remains unclear but is the focus of ongoing investigations. Studies have provided evidence that some of the antibodies detected in CRSwNP polyps are directed against nuclear antigens and cytokines [4950]. How such autoantibodies contribute to the clinical symptoms of CRSwNP remains unclear.

The adaptive immune system is also comprised of T cells that are important not only for their direct cytotoxic functions but also for their ability to mediate an ongoing immune response. In nasal polyps from European patients, a significant fraction of CD4 T cells can produce type-2 cytokines compared to controls, while T cells isolated from nasal polyps from Asian patients are more likely to release type-1 and type-17 inflammatory mediators [38, 43]. Some studies suggest that T regulatory cells are impaired in CRSwNP as determined by reduced levels of the transcription factor Foxp3 and increased levels of SOCS3, a known negative regulator of Foxp3 expression [36, 51]. This imbalance in T regulatory cells could lead to a subsequent lack of immune suppression that in turn could promote the chronic inflammation seen in CRSwNP. However, more research is indicated in this area especially since a study published in 2014 reports that T regulatory cells are increased in nasal polyps [52].

Finally, pathogens can directly and indirectly contribute to CRSwNP pathogenesis. Both *Pseudomonas aeruginosa* and *Staphylococcus aureus* disrupt the epithelial barrier in cultured human nasal epithelial cells [5354]. This impaired barrier could lead to heightened exposure to pathogens as well as increased bacterial colonization. To this end, it is estimated that as many as 63% of CRSwNP patients are colonized with *Staphylococcus aureus* and a subset of

these patients can develop specific IgE antibodies against *Staphylococcus aureus* enterotoxins [55]. Levels of specific IgE significantly correlate with levels of IL-5 and total number of eosinophils in nasal polyps suggesting these antibodies may be important in driving pathogenesis [56].

The sinonasal cavity has a mixture of pathogenic and commensal bacterial and the properties of this microbiome have been explored in CRS, but not specifically in CRSwNP. To date, a reduced diversity of bacteria has been reported in CRS patients compared to healthy controls but no specific organism has yet been linked to causing CRS [5758]. Additionally, traditional pathogenic microbes including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* have been found in sinonasal cavities of patients without CRS, thus obscuring the role these organisms may play in disease [59]. Therefore, further investigations are necessary to fully characterize and define the role of pathogenic and commensal bacteria in CRSwNP.

Genetics

Given the clinical heterogeneity of CRSwNP, the genetics of this disease are not well understood. A 2015 study indicates that first-degree relatives of a patient with CRSwNP have a 4.1-fold increased risk of developing nasal polyps [60]. However, no single polymorphism or genetic mutation has been consistently or reproducibly associated with CRSwNP to date with the exception of the CFTR mutation in cystic fibrosis [61]. For example, filaggrin mutations have been associated with other atopic diseases with epithelial barrier dysfunction including atopic dermatitis and asthma. However, a recent study found no association between presence of a common filaggrin null mutation and CRSwNP [62].

It is tempting to speculate that there is some currently unidentified genetic element responsible for the histologic differences observed between nasal polyps from Asian and Western patients. In support of this concept, a study found that second-generation Asian patients living in the US still had reduced nasal polyp eosinophilia compared to Caucasian or African American patients within the same surgical cohort [63]. However, prospective studies in Asia have suggested that the prevalence of eosinophils in nasal polyps is increasing especially in urban areas [6465]. Taken together, the development of CRSwNP may be dependent on both a genetic predisposition and exposure to specific albeit unclear environmental factors.

Biomarkers

There is no single validated biomarker that can reliably predict if a patient has CRSwNP versus CRSsNP, acute sinusitis, or no sinus disease at all. Eosinophil markers such as ECP, IL-5, or Eotaxin may be useful in confirming CRSwNP but not all CRSwNP patients will have elevated type-2 inflammatory markers and vice versa. There are no biomarkers to date that predict who will respond to medical versus surgical treatment. However, Lou and colleagues reported that having an absolute tissue eosinophil count > 55 eosinophils per high power field or having more than 27% eosinophils out of the entire cells counted in a

sinonasal tissue specimen predicted the recurrence of nasal polyps within 2 years of sinus surgery [66].

When seeking a biomarker, it is important to consider the clinical specimen from which it will be measured. Peripheral blood, while easy to obtain, may not reflect the inflammatory changes observed locally in nasal polyps. A recent study examined if there was a direct correlation between levels of inflammatory mediators measured in nasal lavage fluid versus nasal polyp tissue within the same individuals. Of the 20 mediators evaluated (including ECP, IL-5, IL-13, and eotaxin) only IL-10 was found to have a significant and positive correlation between nasal lavage and polyp tissue[37]. This finding supports a prior observation that there is regional variability in inflammatory mediator expression within a single sinonasal cavity [67]. Therefore, the chronic inflammation in nasal polyps may not necessarily be reflected when sampling the entire nasal cavity by lavage.

Definition of CRS

According to the EPOS 2012 guidelines, CRS is defined as inflammation of the nose and paranasal sinuses characterized by the presence of two or more of the following symptoms for greater than 12 weeks duration: 1) nasal blockage/obstruction/congestion; 2) nasal discharge; 3) facial pain/pressure; 4) reduction or loss of smell [1]. Objective confirmation of the diagnosis is made by sinus CT scan or nasal endoscopy that will also determine the phenotype: CRSsNP or CRSwNP. In adults, nasal polyps should be seen in both nasal passages and any unilateral polyps should be concerning for an alternative etiology such as malignancy.

Recommendation for information to be obtained to determine the phenotype

When evaluating patients for CRSwNP, it is important to evaluate for the presence of the 4 cardinal symptoms: rhinorrhea, nasal congestion, facial pressure/pain, and hyposmia. While not definitive, hyposmia is more classically associated with CRSwNP while facial pain/pressure is more suggestive of CRSsNP [8, 9]. It remains difficult to distinguish eosinophilic and non-eosinophilic nasal polyps by clinical symptoms alone. A recent study examining 57 CRS patients who underwent surgery at a tertiary care facility found that ear pain, sneezing, severe difficulty breathing through the nose, severe nasal congestion, and bothersome loss of taste/smell were significantly more likely to be reported in patients with eosinophilic compared to non-eosinophilic nasal polyps [10]. The duration of sinus symptoms is also critical to ascertain, as symptoms lasting greater than 12 weeks are consistent with chronic rhinosinusitis while those lasting less than 4 weeks are more concerning for an acute infectious process.

In addition to addressing sinonasal complaints, a detailed clinical history should be obtained to establish the presence of an underlying lower respiratory disease such as asthma. Past reactions to any COX-1 inhibitors should be documented so as to not miss the diagnosis of AERD. Finally, symptoms such as sneezing, itching, and ocular involvement are suggestive for underlying allergic rhinitis and should be evaluated given the association with CRSwNP.

Treatment

Medical treatment options for patients with CRSwNP remain limited. According to the most recent US guidelines, both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies for affected patients [68]. Intranasal corticosteroids can decrease nasal polyp size, lessen sinonasal symptoms, and improve patient quality of life [6970]. Oral corticosteroids can also reduce polyp size and improve symptoms but should always be administered cautiously given their association with serious systemic side effects [71]. Antibiotics may be useful in treating infectious exacerbations of CRSwNP, but clinically significant efficacy (*i.e.*, polyp shrinkage) in large, randomized trials is lacking.

Patients with significant sinonasal disease and/or those who fail medical management should be evaluated for sinus surgery. In a retrospective analysis, a delay in over 5 years from initial CRS diagnosis to sinus surgery was associated with greater post-operative health care utilization compared to when surgery was performed within 12 months of diagnosis [72]. Functional endoscopic sinus surgery can improve sinonasal symptoms as well as objective evidence of sinonasal inflammation on sinus CT scan [2273]. However, nasal polyps can still reoccur despite sinus surgery [74] with patients having both CRSwNP and asthma requiring, on average, significantly more sinus surgeries than patients with CRSwNP alone [75].

In 2011, the US Food and Drug Administration approved the use of Propel™ implants, biodegradable stents that elute mometasone over a 30-day period [76–78]. When inserted at the time of sinus surgery, these stents significantly reduced postoperative surgical interventions by 51%, oral corticosteroid use by 40%, and frank nasal polyposis by 46% [79] after 1 month. Given these findings, a longer-lasting variant of Propel™ is currently being evaluated in a FDA trial with initial results suggesting this stent can significantly improve polyp size and nasal symptoms 3 months following insertion [80].

There have also been several promising clinical trials evaluating the safety and efficacy of various biologics in CRSwNP. Notably, these drugs target factors associated with the type-2 inflammation observed in the polyp tissue. Omalizumab, a fully humanized anti-IgE monoclonal antibody, significantly reduced nasal polyp size and improved symptoms when compared to placebo in CRSwNP patients independent of atopic status [81]. In CRSwNP patients with severe nasal polyposis refractory to corticosteroid therapy, mepolizumab, a humanized anti-IL-5 antibody, also significantly reduced nasal polyps and improved sense of smell, post-nasal drip, and nasal congestion (but not rhinorrhea) when compared to placebo treated controls [82]. Finally, dupilumab, a human monoclonal antibody that binds to the IL-4 receptor alpha subunit and inhibits signaling of IL-4 and IL-13, significantly reduced nasal polyp burden and improved nasal symptoms when used in conjunction with intranasal steroids in CRSwNP patients with refractory disease [83]. It should be noted that omalizumab, mepolizumab, and dupilumab are currently not approved for the treatment of nasal polyps. However, given the separate observations that omalizumab, mepolizumab, and dupilumab can also reduce asthma exacerbations [84–86], it is possible that these biological agents could have potentially even greater beneficial effects in patients with both asthma and CRSwNP.

Research questions and future directions

Over the past decade, there have been very important advances made in both the clinical and pathophysiological understanding of CRSwNP. However, many important questions still remain unanswered including:

- What is the true prevalence of CRSwNP within the general population or even among patients with CRS with or without asthma?
- What are the factors (environmental or genetic) that trigger the development of CRSwNP?
- What role does bacteria (pathogenic or commensurate) play in CRSwNP?
- What are the precise cellular and molecular events that lead to epithelial barrier dysfunction and immune dysregulation in CRSwNP?
- What are unique biomarkers in CRSwNP that could serve as targets for potential clinical and therapeutic interventions?
- What are the underlying mechanisms by which omalizumab, mepolizumab, and dupilumab exert their clinical effects?

Conclusion

In summary, CRSwNP is an important clinical entity diagnosed based upon the presence of subjective and objective evidence of chronic sinonasal inflammation. Nasal polyps occur bilaterally within the nasal cavity and are benign in CRSwNP. Men are more likely to be affected than women but no specific genetic or environmental factors have been linked to the development of the disorder to date. CRSwNP is frequently associated with asthma and allergic rhinitis but the cellular and molecular mechanisms that contribute to the clinical symptoms are not fully understood. Defects in the sinonasal epithelial cell barrier, increased exposure to pathogenic and colonizing bacteria, and dysregulation of the host immune system are all thought to play prominent roles in disease pathogenesis. Additional studies are needed to further explore the clinical and pathophysiological features of CRSwNP so that biomarkers can be identified and novel advances can be made to improve the treatment and management of this disease.

Acknowledgments

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Abbreviations

ECP	Eosinophil Cationic Protein
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps

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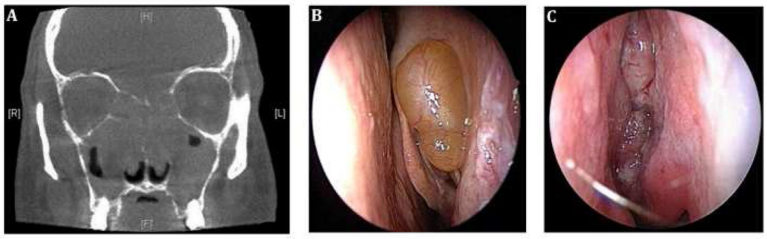

Figure 1. Imaging studies of nasal polyps

Sinus CT scan of a patient with CRSwNP (A). Benign (B) and malignant (C) nasal polyps are directly visualized in the nasal cavity by endoscopy.

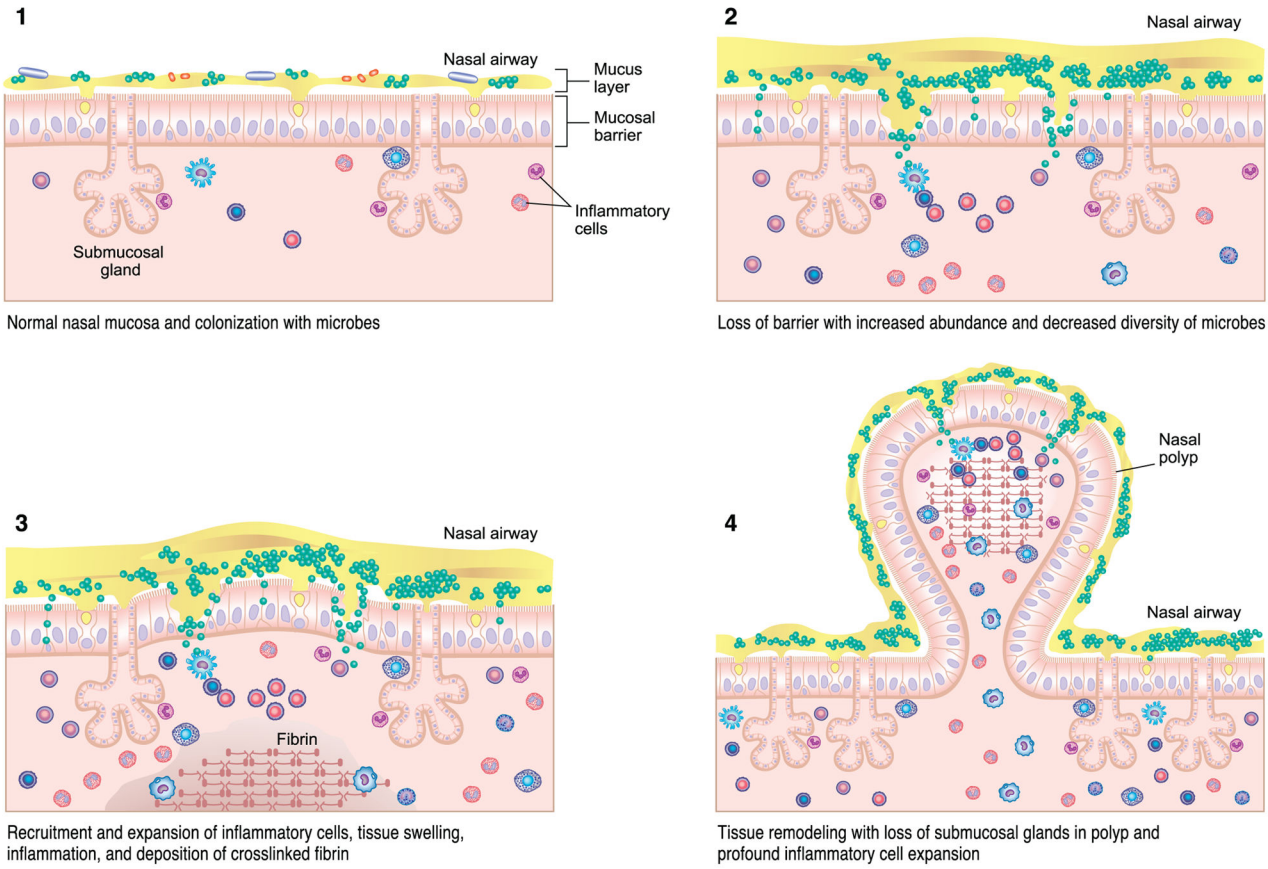

Figure 2. Overview of CRSwNP pathogenesis

Colonization with microbes and accumulation of immune cells can lead to tissue injury, inflammation, and mucosal barrier loss in CRS.