Özlem Önerci Celebi
T. Metin Önerci
Editors

Nasal Polyposis and its Management

Pathogenesis, Medical and Surgical Treatment

Second Edition

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Preface

It is with great pleasure that we present the second enlarged edition of the book "Pathophysiology and Management of Nasal Polyposis." The first edition was accepted with great enthusiasm, received very good feedback. It was sold out. Since its online publication on September 09, 2010, there have been a total of 38,750 chapter downloads for the eBook on Springer Link, and it was among the top most downloaded eBooks in its respective eBook Collection in 2019. There is so much new information that we felt the need to make a second edition.

The success of the book was very much due to great contribution and efforts of Berylin J. Fergusson. She was a great personality, a very good friend, an excellent scholar and researcher. Unfortunately, she passed away. We remember her with great memories and her contributions to our field. After her decease, we have a new coeditor to replace her: Mrs. Özlem Önerci Celebi. Beryll knew her very well, and they were very close friends. Beryll always appreciated her so much and she wanted to include her as a coeditor for the second edition. Therefore, I am happy to realize her wish having her as the coeditor. Rest in peace Beryll, we will always remember you and you will live in our hearts.

Prof. Andrzej Szczeklik from the Department of Medicine, Jagiellonian University School of Medicine, Krakow, Poland, passed away too. For his memory, we have not changed his chapter, the 13th chapter in the first edition "Nasal Polyps and Lower Respiratory Tract Relationship." We will remember him with great respect and dignity.

We hope that the second edition with its new and updated chapters will fill the gap on this topic.

Istanbul, Türkiye — Özlem Önerci Celebi
Ankara, Türkiye — T. Metin Önerci

Acknowledgment

This text is dedicated to the memory of BJ Ferguson who inspired us with her dedication to patient care, innovation, and continuous pursuit of patient-centered ways to solve problems in chronic rhinosinusitis.

Over 20 years ago in her Triologic Candidate's thesis, she was hopeful that we would be able to better unravel the intricacies of CRS:

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CANDIDATE'S THESIS

Eosinophilic Mucin Rhinosinusitis: A Distinct Clinicopathological Entity

Berrylin J. Ferguson, MD

I predict that in the future, genetic and molecular diagnostics will lead to more categories as we unravel the complexity of the disease syndrome of CRS and its large subfamily, eosinophilic CRS. —BJ Ferguson

She understood the concept of "endotypes" before that term was utilized widely in our field and she helped shift the paradigm in the understanding of eosinophilic mucin chronic rhinosinusitis as an inflammatory entity. She was a true scientist, colleague, and friend. In the spirit of BJ, this text seeks to ask the important questions in our field. We are hopeful that this work inspires each of you to ask the important questions that are driven by the complexity and intricacy of our patients.

Contents

History of Nasal Polyposis

Fuad M. Baroody

Core Messages

- Polyps were first reported about 4000 years ago across several civilizations.
- Both diagnosis and treatment underwent a major revolution at the end of the twentieth century with the development of computed tomography scanning and endoscopy.
- Corticosteroids are the most commonly used agents for treatment.

1 Introduction

Nasal polyps were first recorded approximately 4000 years ago. Over the years, there have been significant advances in the understanding of the incidence, epidemiology, and pathophysiology of polyps. The means of diagnosis and medical and surgical treatments have also undergone a major revolution. This chapter reviews the chronological history of nasal polyps, their diagnosis and pathophysiological associations, and the historical milestones that shaped the management of polyps as it is practiced today.

2 The History of Rhinology and Nasal Polyps

The earliest record of nasal polyps is found in the Egyptian literature of approximately 2000 years BCE [1]. Rhinologic procedures dating back to 700 BCE are depicted in ancient Hindu and Egyptian medical texts. One of the great Hindu surgeons, Susruta, who practiced in the fifth century, was the founder of modern-day rhinoplasty and nasal reconstructive flaps. The ancient Egyptians (of 1500 BCE) were known for their familiarity with and dexterity in the nasal cavity as they routinely removed cranial contents through the nose to prevent facial disfiguration during the mummification process. Although Susruta undertook advanced nasal surgical procedures, Hippocrates (460–370 BCE) is better known as the father of rhinology and medicine, due to his influence during the apex of Greek civilization, in approximately the fifth century BCE. In addition to establishing the Hippocratic oath, Hippocrates also observed and documented medical afflictions related to otolaryngology, including coryza, pharyngitis, intubation, uvulotomy, tonsillectomy, nasal fractures, epistaxis, sinusitis, and nasal polyps [2].

Hippocrates referred to the "nasal growths" as "polypus" due to their resemblance to the sea polyp, and this name has persisted to this day [1]. Hippocrates and other renowned physicians, including Claudius Galen, Paulus Aegineta, and Fabricius Hildanus, are known to have treated nasal polyps in their time.

3 Etiology and Pathophysiology

Polyps were initially believed to be due to a state of thickened or viscous bodily humors. In the early first century AD, Celsus and others noted that nasal polyps were affected by moist weather and warm seasons [2]. The theory that these nasal masses were a manifestation of systemic disease prevailed until the early seventeenth century, when local trauma was hypothesized to contribute to the condition. Boerhaave, in 1744, was among the first to surmise that these growths resulted from elongation of the linings of the sinus membranes [1]. About the same time, Manne and Heister suggested that polyps occurred secondary to obstruction of the ducts of mucous glands.

The nineteenth century was also fraught with controversies regarding the etiology of nasal polyps. Virchow [3] and

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his pupils believed that these masses were primary tumors, including myxomas and fibromas. Eggston and Wolff [4] viewed them as passive edema of the mucosa, whereas others believed in an infectious etiology, including sinusitis or osteitis [5]. In 1843, Frerichs and Billroth proposed that polyps were truly hypertrophy of normal sinonasal mucosa, as the epithelium covering the polyp was similar to the mucosa of the originating sinus [1].

A systematic investigation of etiological associations began in the early twentieth century. In 1933, Kern and Shenck proposed a relationship between allergy and nasal polyps [6]. They found that the incidence of nasal polyps was 25.9% in patients with allergic rhinitis compared with 3.9% in a nonallergic population. They also noted that the ethmoid air cell system was the most common target for inflammatory responses and that polyps frequently originated from this site. Eggston's [4] concept of the etiology of polyps is that they arise due to basic vascular changes in the nasal mucosa induced by repeated attacks of sinusitis, periphlebitis, and obstruction of the return flow of interstitial tissue fluid, leading to passive congestion and edema. Advances in immunohistochemistry and immunobiology in the 1940s led to the first description of the predominance of eosinophilic and lymphocytic populations in polyps. Anderson and Bing have shown the polyp stroma to be a proteinaceous exudate, whereas Weisskopf and Burn [7] considered it to have acid mucopolysaccharides. Berdal [8] states that accumulation of reagins and ample edema in polyps is due to allergic inflammation. On the other hand, Tandon et al. [9] observed no difference in the histological appearance of allergic and infective polyps.

Kern and Schenck's initial report of the strong relationship between allergies and nasal polyps has been questioned by more recent investigations. Capllin et al. examined 3000 patients with evidence of atopy and found that only 0.5% had nasal polyps [10]. Following their findings, Bunnag et al. reported an incidence of 4.5% of nasal polyps when 300 patients with allergic rhinitis were examined [11]. These, and other, studies have led most allergists and rhinologists to the conclusion that allergic rhinitis may not be the primary causative factor of nasal polyps. Furthermore, Bonfils et al. have shown that the presence of allergy does not modify the symptoms of nasal polyposis or their response to medical treatment [12]. Several other theories about the etiology of nasal polyps are under investigation today: bacterial infections, mucosal inflammation caused by bacterial superantigens, fungal inflammation, genetic factors (cystic fibrosis, primary ciliary dyskinesia), and aspirin hypersensitivity [11, 13, 14]. The association between cystic fibrosis and polyps was first noted in 1959 by Lurie, and, soon thereafter, Schwamann described its relationship with sinusitis [15].

The medicinal properties of acetylsalicylic acid (ASA) have been known for more than 3500 years. Ancient Chinese, Indian, and Egyptian healers prescribed ASA, as extracts from tree bark and leaves, for a variety of symptoms, including fever, pain, and labor. In 1880, Felix Hoffman, an employee of a dye manufacturing company owned by Friedrich Bayer, used waste components of the factory to synthesize a stable form of salicylic acid powder. Over the course of 1 year, Hoffmann purified the substance until he produced a pure form of ASA. Soon after its introduction in 1899, aspirin sensitivity was reported by Hirshberg, a German physician. As early as 1929, reports of bronchospasm were noted in aspirin-sensitive patients undergoing polypectomy. In 1969, Samter and Beer reported the triad of aspirin sensitivity, nasal polyps, and asthma [16].

4 Diagnosis of Nasal Polyps

Contrary to one's expectation, the historical description of polyps was not limited to those that protruded through the nares or those that caused physical nasal deformity. In the Egyptian literature, Samuel noted that "a polyp shows itself by a bad smell of the nose." Hippocrates describes polyps as "sacs of phlegm that cause nasal obstruction and derange the sense of smell." Celsus likened polyps to "the nipples of a woman's breast" and wrote in his case reports that "large polyps dangled into the pharynx" and "on cold and damp days strangulate a man," depicting large polyps that obstructed the choanae and oropharynx [1].

Visualization of the anterior nasal cavity was enhanced by the development of the nasal speculum. While cauterizing patients for epistaxis, Hippocrates used a crude tubular speculum. A similar prototype of tubular speculum was also used by Hindu Ayurvedic doctors in 500 BCE [2] and by Haly Abbas (940–980), a prominent figure in Islamic medicine. These early speculums were modifications of instruments used for gynecological and rectal examinations. Fabricius Hildanus (1560–1634) constructed an aural speculum, which closely resembles the modern-day nasal speculum. This instrument was molded to its current specifications in the eighteenth century by Peret and Kramer [5].

Sir Morell Mackenzie, who was responsible for establishing otolaryngology as a unique subspecialty, wrote that Levert, a French obstetrician, used a speculum made of polished metal that reflected sunlight to view polyps and tumors of the ears, throat, and nostrils [17]. Until the sixteenth century, candlelight was primarily used to examine the anterior nares. In the 1570s, Aranzii used a glass flask filled with water and candles to intensify the light directed into the patient's nose. In 1829, a young physician named Benjamin Guy Babington presented a series of flat and angled handheld mirrors at the Hunterian Medical Society and demonstrated the ability to reflect sunlight to the back of the pharynx. He also used a tongue retractor to obtain an unob-

structed view. Although Babington did not publish the success of his instrument in viewing the structures of the larynx, other authors over the mid-1800s did mention this device and his techniques [5].

Alfred Kirstein (1863–1922) was responsible for the introduction of artificial light to the field [18]. The instrument consisted of a flat spatula illuminated by a urological head lamp. Subsequently, Kirstein developed the first headlight that remarkably resembles those that are in use today. Perhaps of greatest significance was the advent of both flexible and rigid fiberoptic endoscopes in the late 1900s, which have revolutionized the examination of the upper aerodigestive tract in otolaryngology.

The development of X-ray techniques in the nineteenth century also influenced the diagnostic algorithm of polyps. The Caldwell, Waters', and submentovertex views became essential for identifying the opacification of the sinuses and bony abnormalities. Computerized axial tomography (CAT), which was developed by Hounsfield in 1970, surpassed conventional radiographs and provided superior imaging of the sinuses. Although computed tomography (CT) scans are not essential for the diagnosis of most nasal polyps, they are important for determining the extent of sinonasal disease and for planning surgical treatment.

5 Treatment of Nasal Polyps

The recurrent nature of nasal polyps has been known since the Hippocratic era. Hippocrates wrote about patients who required multiple treatments and recognized that even after performing a directed excision, additional therapy was needed to prevent redevelopment of polyps. Thus, throughout the ages, till today, polyps are treated both medically and surgically.

5.1 Medical Treatment

Hippocrates used nasal packs and tampons coated with honey and copper salts in an attempt to curtail the recurrence of polyps; however, the effects of this treatment are unknown. A Roman physician, Claudius Galen, treated polyps primarily medically with oily applications, goose fat, calf tallow, and irritating medications like turpentine [1]. No further significant descriptions of the medical management of polyps were found until the twentieth century [19].

Kern and Schenk's description of the relationship between allergies and polyps paralleled the discovery that histamine caused allergic reactions. The Italian pharmacologist Daniel Bovet synthesized antihistamines during much of the 1930s, and, in 1944, the first nontoxic antihistamine became available to the public. Thus, antihistamines were used as a primary and postsurgical treatment for polyps. Evidence of a helpful role of antihistamines in nasal polyposis is lacking, and they are now primarily used to treat concomitant allergic rhinitis, if present. The current mainstay of medical therapy is corticosteroids.

The discovery of steroids represented a new era of treatment. Anabolic steroids were first isolated and chemically characterized during the 1930s, and topical and systemic steroids have been used for the management of nasal polyps since the 1970s [20, 21]. Van Camp was one of the first to describe the use of preoperative oral steroids to shrink the polypoid tissue and facilitate removal [21]. Although the efficacy of a short course of systemic steroids is well-established, the benefit is short-lasting as the polyps recur slowly after discontinuation [22]. The addition of intranasal steroids after a course of systemic steroids minimizes recurrence and maintains medical control of the polyps [23]. Intranasal steroids are also very frequently used as the initial treatment of nasal polyposis and have been shown to reduce the size of polyps, delay recurrences, and decrease the need for repeat surgery [24].

More recently, and because of our evolving knowledge of the pathophysiology and the recognition that T helper 2 (Th2) cell-mediated inflammation is central to the genesis and maintenance of nasal polyps in many patients, biological therapies are being investigated and approved for the treatment of nasal polyps. Anti-immunoglobulin (Ig)E, and anti-interleukin (IL)-5 have been shown to be effective in decreasing polyp size and are being investigated in large clinical trials [25, 26]. Dupilumab, a monoclonal antibody against the alpha subunit of the IL-4 receptor that inhibits the effects of both IL-4 and IL-13, has also shown to be highly effective in the treatment of chronic rhinosinusitis with polyposis and has already been approved by the Food and Drug Administration (FDA) for use in the United States [27].

5.2 Surgical Treatment

The history of the surgical treatment of polyps is most intriguing and gruesome. In the treatises, Hippocrates delineated several methods he used to remove polyps. One method involved using a soft sponge, large enough to fill the nasal cavity that was fastened to several pieces of string. Then, a forked flexible metal probe was passed through the nostrils and into the pharynx with the strings tied to the forked end of the probe. The sponge was then pulled through the oral cavity, pushing the polyps out [1]. The sponge method was used to remove polyps until the 1880s. For larger polyps, Hippocrates used a crude snare by fashioning a loop of sinew around the base of the polyps and passing one end through the pharynx, which effectively avulsed the polyps (Fig. 1). He also used a hot iron passed through the nostrils to cauter-

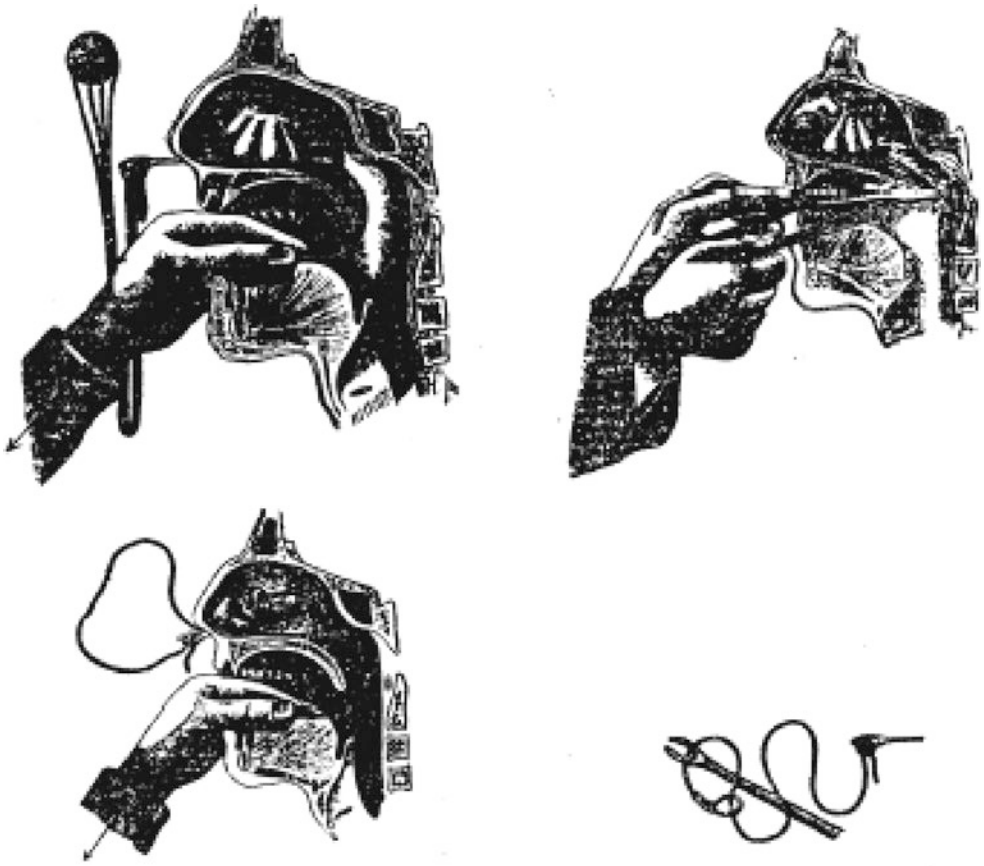

Fig. 1 The Hippocratic method of excision of nasal polyps. The loop is inserted intranasally, the polyps are avulsed from their base, and then removed from the pharynx. (Adapted from Stevenson and Guthrie [6])

ize polyps. After these treatments, Hippocrates placed stents smeared with oil, honey, and copper powder in the nasal cavities [1].

Roman medicine was dominated by Aulus Cornelius Celsus, also known as the Roman Hippocrates, who wrote the book series *De Medicina*. Celsus frequently treated polyps with caustic agents but also used a sharp spatula-like instrument to separate the polyp from the bone and removed it with a hook-like instrument from the nose [2]. The "knotted-string method" was utilized in the sixth and seventh centuries by Paulus Aegineta, who wrote: "taking a thread of moderate thickness, like a cord, and having tied knots upon it at a distance of two or three finger breadths, we introduce it into the nose via a double headed speculum upward to the ethmoid openings, then drawing it with both hands, we saw away … at the fleshy bodies." In the pre-Renaissance period (1000–1200s), Rolando, a famed Italian physician, also used the knotted string and the spatula methods to remove polyps [2].

Not much changed in the surgical methods until the 1600 and 1700s, when snares and forceps were developed. Although Fallopius (1523–1562) is credited for developing the snare, medical specialists from Japan and India were using snares even prior to that. Fallopius wrote, "I take a silver tube which is neither too narrow nor too broad and … brass wire, sufficiently thick, preferably the wire with which harpsichords are made. This doubled I place in the tube so that from this wire a loop is made at one end of the tube, by which, used in the nares, I remove the polyp. When the polyp is engaged in the loop, I push the tube to the root of the polyp, and then pull on the metal threads and thus I constrict the roots of the polyp and extract it …" [1]. The forceps, first introduced by Fabricius in the mid-1600s, were actually scissors curved at the end. John Van Horne (1621–1770) added teeth at the point of the instrument to provide a better grip on the polyps. Benjamin Bell, the eighteenth century prominent Scottish surgeon, published in *A System of Surgery* (1791), a range of snares and forceps to remove polyps [1, 2]. Many modifications of the forceps ensued over the following years (Fig. 2). For larger polyps, surgeons described splitting the nasal alae and sometimes even the soft palate. The advocates of these procedures maintained that these open approaches

offered better visualization and, thus, more complete excisions of the polyps [2, 5].

Throughout the eighteenth and nineteenth centuries, the struggle in treating primary and recurrent nasal polyposis continued. Until the use of endoscopy became popular, more extensive intranasal procedures such as Caldwell-Luc radical antrostomy, intranasal ethmoidectomy, and external frontoethmoidectomy were also utilized. These procedures stripped the mucosa and altered the nasal and paranasal sinus landmarks [28]. Even with such extensive intervention and medical therapy, polyp recurrence was still a problem.

Significant changes in sinonasal surgery were brought about with the development of endoscopic sinus surgery (ESS). Although the term "endoscopy" was coined by the French urologist Antonin Jean Desormeaux (1815–1894), it was the German physician Phillip Bozzini who developed the first endoscope, known as the "Lichtleiter," in 1805 [17]. The instrument consisted of an eyepiece and a container for a candlelight that was reflected by a mirror through a tube. Bozzini used his rudimentary endoscope to examine the bladder, rectum, and pharynx. Another German urologist, Max Nitze, modified the "Lichtleiter" by creating a metal tube with a series of lenses within. Several water-cooled platinum wires were threaded through the tubes and used as the light source. In 1950, Storz introduced the first fiberoptic endoscope that bears resemblance to those used today [17]. Hirshmann, in 1901, first applied endoscopy to sinonasal disease. He modified a cystoscope and used it to view the maxillary sinus and middle meatus through an enlarged dental alveolus. Despite the technological advancements, it was not until the 1960s that the endoscope gained popularity for the diagnosis and surgical treatment of sinonasal diseases. This newfound interest was due in part to the increasing popularity of minimally invasive intervention in all surgical specialties and in part to the works of Walter Messerklinger of Graz, Austria. His work involved the anatomical and physiological study of the nose and paranasal sinuses and their mucosal blanket. Most importantly, he noted the patterns of mucus clearance of different areas of the nose and sinuses through various ostia and into the infundibulum and that disruption of the mucociliary transport or obstruction of normal flow led to disease. With Messerklinger's discoveries, functional endoscopic sinus surgery (FESS) was introduced in the late 1960s in Germany, and David Kennedy is credited for introducing FESS in the United States in 1985 [29]. Several advances to FESS have evolved since its introduction, including the use of microdebriders and CT-guided surgery, which have improved the speed and safety with which these procedures are performed.

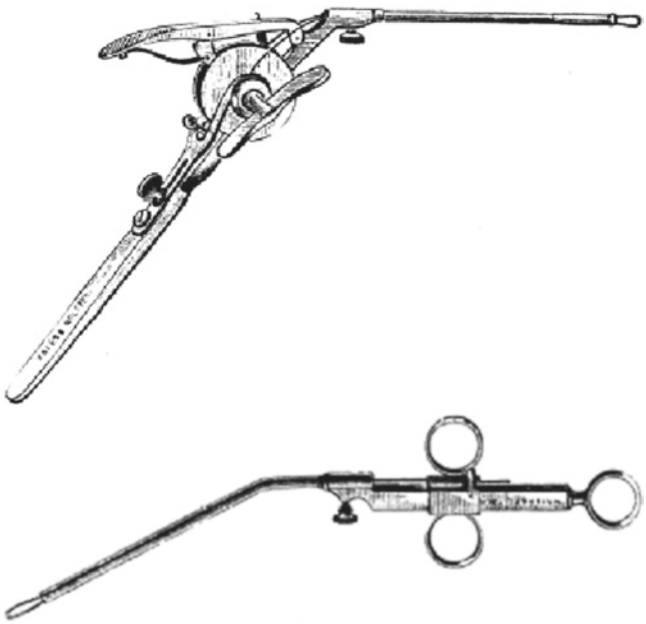

Fig. 2 The general design and function of modern-day snares closely resemble those illustrated here. The McKenzie (top) and Krause (bottom) snares were developed in the late 1700s. (Adapted from Lack)

6 Conclusions

Nasal polyps have been recognized for a long time.

Although many theories about their cause have evolved over the years, we are still left with controversy and uncertainty about their etiology. The diagnosis and treatment strategies have undergone a colorful evolution. Today, we have overcome most of the difficulties in the diagnosis and have significantly improved the technical aspects of surgical treatment. Nevertheless, we still face recurrent disease and the need for repeat surgical procedures. Thus, to this day, the quest for the cure of nasal polyps remains an important goal.

Take-Home Pearls

- Polyps was first reported several centuries ago.
- The relationship between nasal polyps and allergy has been questioned recently.
- The mainstay of medical therapy is systemic and intranasal steroids.
- The mainstay of surgical therapy is endoscopic, intranasal removal of polyps with functional sinus surgery.

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Epidemiology of Nasal Polyps

Derek Wu, Rakesh K. Chandra, David B. Conley, and Robert C. Kern

Core Messages

- The prevalence of nasal polyps (NPs) in the general population has been grossly estimated to be 1–4%.
- An association between NPs and allergic rhinitis (AR) is weak, with NP prevalence in patients with AR estimated to be between 1.5% and 1.7%, similar to that of the general population.
- Large cohort studies have revealed a strong association between asthma and NPs.
- The incidence of NP increases with age and is likely the greatest between 40 and 60 years of age.
- If NPs are found in a child, then a workup for cystic fibrosis should be conducted.
- Genetic inheritance has been proposed as a possible etiology of NPs but remains unclear.
- Up to 50% of aspirin-intolerant patients have NPs, and up to 36% of patients with NPs may have some form of analgesic intolerance.
- Allergic fungal rhinosinusitis is an established phenotype strongly associated with NPs.
- Ethnic and geographic variation has emerged as a potential modifier in NP pathophysiology.

1 Introduction

Phenotypically, chronic rhinosinusitis (CRS) can be classified as either CRS without NPs (CRSsNPs) or CRS with NPs (CRSwNPs). Mounting evidence suggests that a nasal polyp (NP) is a clinical manifestation of multiple coexisting immunologic pathways and, because the nature of this entity is likely heterogeneous, its epidemiology is difficult to characterize. Nasal polyps are composed of an edematous tissue that projects from the ethmoid sinuses and are composed of a fibrin matrix [1]. Although the majority of CRSwNP cases are idiopathic, a minority are associated with a distinct genetic, immunologic, or metabolic defect, and these cases will be discussed below. From the perspective of inflammatory mechanisms or endotypes, CRSwNPs, in general, reflect more type 2 (eosinophilic) inflammation in comparison to CRSsNPs, particularly in Western patients [2]. Asian patients have higher levels of type 1 and type 3 inflammation, but the end result is still a cross-linked fibrin matrix with tissue edema [3]. Furthermore, CRSwNPs must be differentiated from antrochoanal polyps, which are also idiopathic, but account for only 5% of polyp cases [4]. Antrochoanal polyps are usually unilateral and solitary and most often arise from the maxillary sinus. This is a distinct disease process that often presents at a younger age compared to CRSwNPs. In contrast to CRSwNPs, antrochoanal polyps reveal lesser degrees of eosinophilia with a more normal-appearing mucosal surface and basement membrane [5].

The prevalence of NPs, in particular, can be difficult to ascertain, as mentioned previously. The lack of easy screening tools, the inconsistent use of diagnostic metrics and clinical definitions by medical professionals (specialty and non-specialty providers), and the failure to subclassify CRS during population analysis all likely contribute to this conundrum. These limitations notwithstanding, a few population-based studies to date offer a glimpse of the epidemiology of

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NPs that continues to be refined. The prevalence of NPs in the general population has been grossly estimated to be 1–4%, though supporting evidence for this finding is scarce [4]. Older reports have suggested a prevalence ranging from 0.2% [6] to 2.2% [7], and autopsy studies have reported the prevalence of bilateral NPs to be 1.5–2% [8]. A Swedish study found that the prevalence of NPs was 2.7% (95% confidence interval (95% CI) = (1.9–3.5)) in their cohort where nasal endoscopy was performed on 1387 adult volunteers [9]. A study conducted in the United States revealed 83 (±13) CRSwNP cases per 100,000 person years using physician-entered diagnostic codes on 446,480 electronic health records over a 7-year period [10]. In France, Klossek et al. used a validated questionnaire and estimated nasal polyposis prevalence to be 2.11% (95% CI = 1.83–2.39) in a cohort of 10,003 random subjects [11].

Various comorbidities such as allergic rhinitis (AR), generalized atopic status, gastroesophageal reflux disease (GERD), and asthma have all been studied with regard to the genesis of NPs. Variations in prevalence have also been reported as a function of demographic factors, including age and gender. In addition, hereditary factors and ethnic variations exist and must be considered. This chapter will describe the epidemiology of CRSwNPs in general and in the context of comorbid disease states and known underlying pathophysiologic processes of sinonasal inflammation.

2 Allergy

Historically, NP formation was suggested to be a product of an excessive allergic response (atopy) to inhalant allergens. Although this relationship seemed intuitive, current data suggest that this association is weak. NP prevalence in patients with AR is estimated to be between 1.5% [12] and 1.7% [13], and this prevalence approaches that of the general population, as previously described. The relationship between nasal polyposis and allergy has been extensively studied and widely debated. Studies have examined how factors such as NPs and atopy may correlate with CRS severity, as measured by computed tomography (CT) scanning. In a group of 193 CRS patients treated at a tertiary care center, statistical analysis revealed that atopy was significantly more prevalent in the CRSsNP subgroup (32.3%) compared to the CRSwNP subgroup (27.5%). Although the mean Lund–Mackay score was slightly greater in atopic patients compared to nonatopic individuals (14.2 vs. 12.3, $p = 0.05$), significance was lost when the cohort was separated into those with and without NPs. In contrast, increased radiologic severity was observed in the CRSwNP group. Overall, these data suggest that the presence of NPs is unrelated to atopy and is a better predictor of advancing radiologic disease [14].

A similar study examined 106 patients from a tertiary care center of which 49% were atopic by skin endpoint titration. Overall, both atopic and nonatopic patients exhibited no difference in the prevalence of NPs (38% and 37%, respectively). The presence of asthma, however, was an independent predictor for the existence of NPs, which was observed in 57.6% of asthmatics and in 25% of non-asthmatics ($p = 0.0015$). As with previous reports, the Lund–Mackay score was the greatest in nonatopic asthmatics, followed by atopic asthmatics, and then non-asthmatics. As expected, the Lund–Mackay score was the greatest in the polyp group, but it is important to note that this association was found to be independent of atopic status. In summary, these data indicate that asthmatic patients are more likely to have polyps than are non-asthmatics [15]. Furthermore, the presence of asthma and polyps are each significant predictors of disease severity as measured by the Lund–Mackay score. In contrast, atopy appears unrelated (or perhaps weakly related) to either polyp growth or advancing severity of radiologic disease.

It is noteworthy that the most robust study to date on the relationship between atopy and polyposis is a systematic review conducted by Wilson et al., whereby the role of allergy in CRSwNPs and CRSsNPs is examined [16]. Out of the 18 studies identified that specifically studied the relationship between CRSwNPs and allergy, 10 showed a correlation, 7 showed none, and 1 was equivocal. It is also worth noting that no articles examined the outcomes of CRSsNPs or CRSwNPs following allergy treatment. Due to the heterogeneous nature of the studies and the poor level of evidence, no definitive association was made for the role of allergy in either CRSwNPs or CRSsNPs. Additionally, in 2016, Li et al. prospectively studied 210 patients with CRSwNPs and found no association between atopy status and either disease severity or their rate of recurrence [17].

The lack of clearcut data is likely rooted in our evolving characterization of CRS as having distinct biologic subtypes and therefore showing variable association with different risk factors. To illustrate this point, in a retrospective study conducted by Marcus et al. in 2019, allergy was found to be more prevalent in distinct phenotypes of CRSwNPs such as allergic fungal rhinosinusitis (AFRS), nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD), and central compartment atopic disease (CCAD) [18]. Similar findings were found in a large-scale, cross-sectional study in the UK by Philpott et al., who concluded that the prevalence of asthma and allergy in CRS varies by phenotype, with CRSwNPs and AFRS having a stronger

association with both [19]. Given the ongoing efforts to synthesize data, expert opinion today posits that allergy testing and treatment is an option in CRSwNPs and CRSsNPs [2].

3 Asthma

In contrast to allergic rhinitis, large cohort studies have revealed a consistently strong association between asthma and NPs. In one investigation of more than 2000 patients, Settipane reported that NPs were more common in nonallergic asthmatics than in allergic asthmatics (13% vs. 5%, $p < 0.01$) [20]. These data were corroborated by Grigoreas et al., who analyzed 3817 Greek patients with chronic rhinitis and asthma [13]. Overall, the prevalence of NPs in this population was 4.2% and NP prevalence was the greatest in nonallergic asthmatics than in allergic asthmatics (13% vs. 2.4%). Another large epidemiological study in Europe conducted by The Global Allergy and Asthma Network of Excellence (GA(2)LEN), which included 52,000 adults spanning 12 countries, further noted an association between asthma and CRS, though the status of polyposis was not specially queried [21]. The study by Philpott et al. that examined 1470 subjects from the UK, however, was able to further stratify CRS by phenotype in their study cohort, citing that the prevalence of asthma as 9.95%, 21.16%, 46.9%, and 73.3% in the control, CRSsNP, CRSwNP, and AFRS group, respectively [19]. Similarly, a population-based study conducted in Taiwan found that asthma was associated with an increased risk of both CRSwNPs and CRSsNPs in their analysis of 81,462 patents, mast cells, and $CD4^+$ T lymphocytes [22]. Bachert et al. theorized that the relationship between severe CRS and asthma may be due to the production of inflammatory cytokines in airways, which induce the upregulation of eosinophils, mast cells, and basophils by bone marrow upregulation. These inflammatory cells then migrate to the airway mucosa, resulting in a reactive inflammatory response leading to NP formation [23].

4 Gender and Age

It has been suggested that the incidence of NPs increases with age [20]. Settipane reported that NP frequency reaches a peak in patients who are 50 years and older [20]. Furthermore, he reports that asthmatics over 40 years of age are four times more likely to have NPs than are those under 40 (12.4% vs. 3.1%, $p < 0.01$) [20]. Larsen et al. reported similar results in a uniform population of Danish patients. Of 252 patients, they observed that NPs were most common in patients who were 40–60-years-old. Additionally, patients over 80 years of age were unlikely to have NPs. The mean age of diagnosis of NPs was 51 years in males and 49 years in females. Similarly, Tan et al. reported increasing rates of NPs with age, citing the highest incidence in the 45–55-year-old group [10], not dissimilar to the results from the UK epidemiological study by Philpott et al., where the mean age for CRSwNPs was 56 years [19]. A study in Korea surveying 28,912 adults also noted a trend of NPs associated with increasing age, peaking at a prevalence rate of 4.8% in the seventh decade of life [24]. In sharp contrast, unilateral antrochoanal polyps were diagnosed at a much younger age: males 27 years and females 22 years [4].

The discovery of NPs in children is extremely rare. The estimated prevalence of NPs in patients less than 16 years of age is 0.1–0.216% [4]. In a study of 1051 pediatric allergic patients, only 1 had NP [12]. If NPs are found in a child, then a workup for cystic fibrosis (CF) should be conducted.

The literature varies in relation to the impact of gender on the development of NPs. In Settipane's review of 211 NP patients, there was an equal distribution of males and females, i.e., 50.2% and 49.8%, respectively [12]. Data published using the Danish National Health Care insurance system to identify patients treated for NPs differ with this prior observation. In fact, this cohort exhibited an increased incidence of NPs in males over 20 years as compared to age-matched females. The male:female ratio of patients with NPs was 2.9 in the ages of 40–50 and was maximal at 6.0 for patients between 80 and 89 years of age [4]. The incidence was the greatest in both males and females in the age range of 40–69 years. In this group, NPs were present in 1.68 male and 0.82 female patients per 1000 annually. It is important to note that data from this Danish study represent a homogeneous population of 252 NP patients culled from 5 years of retrospective data. More recently, Tan et al. have also found a higher prevalence of CRSwNPs in males compared to females (54% vs. 45.5%) in their large population study of primary care patients over a 10-year period in the United States [10]. Similarly, a large, cross-sectional study from Korea consisting of data from 2008 to 2012 showed a similar male preponderance for CRSwNPs [24]. Data from the Korean National Health and Nutrition Examination Survey consisted of 28,912 adults, where the prevalence rates of CRSwNPs and CRSsNPs were 2.6% and 5.8%, respectively. A predominance of male sex was noted in CRSwNPs (odds ratio (OR) (95% CI) = 2.11 (1.90–2.14), $p = 0.01$). Furthermore, the UK study by Philpott et al. also noted a staggering 67.7% male preponderance in their cohort of 651 subjects with CRSwNPs [19]. Overall, the data support a male predominance for CRSwNPs.

5 Genetics

Genetic inheritance has been proposed as a possible etiology of NPs. Studies have suggested that up to 14% of patients with NPs have a family history of the disorder [25]. Attempts to delineate a hereditary pathway using monozygotic twin studies have yielded mixed results. In a report of twins with steroid-dependent asthma, only one had bronchospastic aspirin intolerance and NPs, whereas the other did not manifest these phenotypic traits [26]. Further attempts have been made to show an association between NPs and a familial history of the disorder. In a cohort of 174 NP patients, 25% had a first-degree relative with polyps (a parent, sibling, or child) [27]. A total of 44 patients manifested Samter's triad (aspirin intolerance, asthma, and NPs), and 36% of these patients had a first-degree relative with NPs. Furthermore, 32% [28] of the polyp patients had both NPs and asthma, of which 30% had a first-degree relative with polyps. In 2015, a population study using a genealogical database demonstrated a significant familial component in the pathogenesis of both CRSwNPs and CRSsNPs [29]. In a cohort of 1638 CRSwNP subjects, first-degree relatives had a 4.1 increased risk of also having NPs ($p < 0.001$) and, for second-degree relatives, a 3.3-fold increase ($p < 0.004$). Environmental factors are likely particularly important in CRSsNPs, since the spouses of affected patients are two times more likely to also exhibit CRSsNPs, a relationship not seen with CRSwNPs [29]. Another study noted lower eosinophilia in NPs that were surgically removed from second-generation Asian Americans in the United States, a histologic finding more consistent with those seen in Asian patients in their respective, native countries rather than in their Caucasian counterparts living in the United States [30]. Overall, these studies suggest that while genetic factors are likely significant in the development of CRSwNPs, there are rarely clear Mendelian inheritance patterns and a gene–environment interaction is likely at work in familial cases, with multiple genes playing a role.

Identifying the key genes involved in polyp formation remains a work in progress, but three genetic diseases are associated with a high incidence of nasal polyposis: cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and Young's syndrome. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. The gene product of CFTR is a chloride ion channel primarily expressed in the exocrine glands of the lungs, liver, pancreas, and intestines. Approximately 20% of patients with CF have NPs [20]. A diagnostic workup for CF should be conducted in any patient under the age of 16 who presents with NP. Primary ciliary dyskinesia (PCD), also known as Kartagener's syndrome, is characterized by CRS, bronchiectasis, and situs inversus (reversal of the internal organs). Defects in the dynein arms of cilia are primarily responsible for the immotility seen on mucosal biopsy; however, radial spoke defects and microtubular transposition anomalies have been identified [31]. Ultimately, the frequency of ciliary beat is abnormal and uncoordinated. PCD has been seen in both men and women, leading investigators to conclude that this is an autosomal recessive disorder. However, recent observations of a nonconsanguineous family with retinitis pigmentosa (RP) and PCD have suggested an X-linked inheritance pattern [32]. It is likely that there may be more than one mode of inheritance pattern for PCD as investigations into left–right axis deviations in vertebrates have shown an autosomal dominant, recessive, and X-linked pattern [33, 34]. Young's syndrome is another disorder characterized by recurrent sinopulmonary disease, obstructive azoospermia, and NPs [35]. This disease differs from CF and PCD, in that sweat chloride tests are normal, as is ciliary function demonstrated by normal sperm tails and tracheal biopsies. Spermatogenesis is normal, and azoospermia results from an excess of inspissated secretions in the epididymis. The prevalence of Young's syndrome remains unclear, but it has been suggested to be responsible for up to 7.4% of male infertility [20]. Recent advances in the scientific study of genetics have now afforded the possibility of identifying which genes contribute to the development of idiopathic CRSwNPs as well. Genome-wide association studies (GWASs) conducted via a combined Iceland and UK database have shown several markers associated with NPs and CRS [36]. Chief among them was the discovery that a loss-of-function variant in *ALOX15* confers a protective effect on both NPs and CRS. *ALOX15* encodes the enzyme 15-LO, which is implicated in the pathogenesis of NPs. According to Kristjansson et al., the missense variant p. Thr560Met in *ALOX15* is found to be carried by 1 in 20 Europeans and is associated with a 68% reduction of risk of NPs (OR = 0.32) and a 36% reduction of risk of CRS (OR = 0.64) [36]. Such a mutation inactivates 15-LO, an enzyme that converts arachidonic acid to eoxins in mast cells and eosinophils, which are known to be pro-inflammatory metabolites associated with NPs, asthma, and NERD. This knowledge may pave way to future targeted therapeutic interventions, as currently no pharmaceutical agents targeting 15-LO have been approved at the writing of this study.

6 Churg–Strauss Syndrome (CSS)

As a systemic vasculitic disorder, Churg–Strauss syndrome (CSS) commonly presents with upper airway symptoms. Originally believed to be comprised of four hallmark characteristics, namely, bronchial asthma, CRS, eosinophilic vasculitis, and granulomas [37], there is likely phenotypic variation to this syndrome. The American College of

Rheumatology accepts six primary characteristics of CSS: asthma, eosinophilia >10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. To qualify for a diagnosis of CSS, four of the six criteria should be present, yielding a sensitivity of 85% and a specificity of 99.7% [38]. CSS is systemic vasculitis of small-to-medium-sized vessels and is associated with AR and/or CRS with or without NPs [39, 40]. The exact mechanism of CSS is unknown, but eosinophil activation likely plays a major role [39]. Otolaryngologic manifestations may consist of AR, CRS with or without NPs, nasal crusting, otitis media, and, rarely, sensorineural hearing loss and unilateral facial palsy [39]. NPs are present in up to 60% of patients with CSS and are the likely indicators of early disease [40]. Corticosteroids are highly effective in treating patients with NPs associated with CSS [40]. Biologic therapies also offer an emerging option.

7 Intolerance to Nonsteroidal Anti-inflammatory Drugs

NPs are frequently observed in patients who are intolerant to cyclooxygenase-1 (COX-1) inhibitors such as aspirin (acetylsalicylic acid) or nonsteroidal anti-inflammatory drugs (NSAIDs). In this phenotype, NSAIDs induce an acute asthmatic response within 30–90 min of ingestion [41]. This "triad" of symptoms (bronchial asthma, CRSwNPs, and NSAID intolerance) has historically been described using many names, including Samter's triad, ASA triad, aspirin-exacerbated respiratory disease (AERD), or aspirin-induced asthma. Today, they are commonly referred to as nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease or NERD [42]. Despite the myriad names, they all describe the same constellation of symptoms that originate from a dysregulated pathway of eicosanoid synthesis, culminating in eosinophilic inflammation of sinonasal mucosal membranes and a shift toward leukotriene production that is further exacerbated by cyclooxygenase (COX)-1 inhibitors (aspirin or NSAIDs) [2].

In a significant percentage of affected patients, aspirin administration elicits an acute bronchial response with rhinorrhea and nasal obstruction [43]. Aspirin intolerance that causes urticaria without bronchospasm has not been associated with NPs. It has been estimated that up to 50% of aspirin-intolerant patients have NPs and that 36% of patients with NPs may have some form of analgesic intolerance [20]. However, while considering all the patients undergoing endoscopic sinus surgery (ESS), including CRS with and without NPs, approximately 4.6% had NERD [44].

The development of a fully realized NERD likely occurs over time. Initially, patients may present with chronic rhinitis. Within 5–10 years, aspirin-induced asthma will become apparent. Shortly thereafter, NPs become prominent [45]. Nonallergic rhinitis with eosinophilia syndrome (NARES) has been proposed as a precursor to the pathway leading to the ASA triad [46, 47]. It has been shown that NP epithelial cells from NERD patients have abnormalities in basal and aspirin-induced generation of eicosanoids (products derived from arachidonic acid metabolism, including prostaglandins, thromboxanes, and leukotrienes), ultimately leading to aspirin sensitivity [48].

The NPs of NERD patients likely represent a unique phenotype of severe inflammation, which is more recalcitrant to both medical and surgical intervention [49]. These NPs demonstrate increased edema and inflammatory infiltrate compared to those of aspirin-tolerant patients [50]. Additionally, NERD patients' response to surgery is universally poor, undergoing approximately 10 times as many ESS procedures as that of ASA-tolerant patients [44, 51]. Furthermore, NERD patients have a significantly higher rate of symptom recurrence (nasal obstruction, facial pain, postnasal drip, and anosmia), regrowth of NPs at 6-months of follow-up [44, 50, 51], and lack of statistical improvement in forced expiratory volume (FEV1) [50].

8 Gastroesophageal Reflux Disease (GERD)

Among the comorbid conditions associated with NPs, the role of gastroesophageal reflux disease (GERD) is being increasingly scrutinized. There are several hypotheses that explain the association between NPs and GERD. One is the disturbance in sinonasal epithelium barrier function as a direct effect of the refluxate, which is composed of acid, pepsin, trypsin, and bile [52]. A recent systematic review by Leason et al. has shown that there is a strong association between CRS and GERD; however, their meta-analysis was indiscriminate of polyposis status [53]. With respect to individual studies looking at a pathogenic link between CRSwNPs and GERD by proxy of *Helicobacter pylori* detection in polyp samples, most are small, underpowered, and conclude with divergent findings [28, 54–59]. From an epidemiological standpoint, Tan et al. found that GERD was more prevalent in CRSwNPs (176/595, 29.6%) and CRSsNPs (2220/7523, 29.0%) than in controls (1666/8118, 20.5%), with a strong epidemiological association (CRSwNPs vs. controls: OR = 1.5 [1.2–1.8]) [10]. Lin et al. found that GERD patients are 1.85 times more likely to be diagnosed with CRSwNPs after controlling for age, sex, and comorbidities (95% CI = 1.37–2.48; $p < 0.001$) [52]. They did not, however, account for the potential confounding effect of proton pump inhibitor (PPI) therapy on CRS development.

Further studies are needed to elucidate the precise role of pathogenesis that GERD plays in the development of NPs.

9 Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NPs. Classically, a diagnosis of AFRS is made when the following five hallmark characteristics are present: type 1 hypersensitivity to dematiaceous fungi, NPs, paranasal CT scan findings of inspissated mucus with calcification, eosinophilic mucus containing Charcot–Leyden crystals without fungal invasion into the surrounding sinus mucosa, and positive fungal stains from sinus contents [60, 61]. Intraoperatively, the eosinophilic mucus is inspissated and tan-colored with a thick sticky consistency. Rarely does a patient with suspected AFRS satisfy all five of these criteria. However, the diagnosis can be made based on clinical suspicion and intraoperative observations of eosinophilic mucus with fungi and NPs. Staining for fungal elements in intraoperative biopsies has proven to be inconsistent even in patients who are strongly suspected of having AFRS.

The incidence of AFRS has not been well-established, but patient characteristics likely influence disease manifestation. Approximately 5–10% of CRS with NP patients have AFRS [60, 62]. This is typically a disease of younger adults, with a mean age of diagnosis between 22 [63] and 28 years of age [64], which is significantly lesser than that observed in non-AFRS patients. Studies have suggested that there is an increased prevalence of AFRS in southern, more humid climates. Recent reports have suggested that a lower socioeconomic status may also play a role. In patients treated at a tertiary medical center in South Carolina, a significant proportion of the AFRS patients (24.1%) were uninsured or Medicaid recipients as opposed to 5.2% of the non-AFRS CRS patients with NPs. Furthermore, a significant portion of the AFRS group was African American (61.1%) who resided in counties with a greater African American population and more advanced poverty status [64]. These data raise the point that although AFRS may be more prevalent in various ethnic groups, socioeconomic status may also be a factor, in that African Americans accounted for a significant portion of the un- or underinsured. It may be possible that a lower socioeconomic status and, thus, lack of access to health care, may have allowed for disease progression in this series.

10 Ethnicity and Geography

As the exact mechanism of NP formation remains a topic of investigation, ethnic and geographic variation has emerged as a potential modifier in the pathophysiology of NPs. In a Caucasian population, NPs have been shown to have strong type 2 inflammation, with large numbers of activated eosinophils and mast cells [2]. Interestingly, this increase in type 2 inflammation and eosinophils in NPs is not consistent across various ethnicities. In Asian countries, NPs show a more neutrophilic pattern rather than the previously discussed eosinophilic predominance [65]. Yet, the clinical manifestations of NPs remain similar between Asians and Caucasians. Zhang et al. attempted to further characterize the variations seen in Asian polyps. Polyp tissue samples from 27 Chinese patients from the Guangdong province of China were harvested. As with similarly affected Caucasian patients, most of the Asian patients had been treated with nasal steroids and antibiotics. Some had received Chinese herbal medicines. The samples were compared to a group of matched Caucasian Belgian patients, where Chinese polyps had a significantly lower incidence of eosinophils ($p < 0.01$) [66]. A Korean cohort showed a similar preponderance of noneosinophilic NPs [20]. In this study of 30 NP patients, not only were 66.7% noneosinophilic, but the basement membrane thickness of the polyps was found to be significantly thinner in the noneosinophilic than in the eosinophilic group (8.2 ± 3.5 vs. 13.9 ± 4.5 μm) [67]. Although the predominant inflammatory cellular infiltrate differs between Caucasians and Asians, commonalities are also apparent. Zhang et al. [66] reported that 10 of the Asian polyps contained immunoglobulin (Ig)E against *Staphylococcus aureus* enterotoxins (SAE), which is consistent with the previously reported data that one-third of Caucasians with NPs and asthma have IgE against SAE [68]. As in white subjects, tissue IgE and soluble IL-2R (sIL-2R) are elevated in Asian polyps. The eosinophilic infiltrate is decreased in Asian polyps as measured by eosinophil cationic protein (ECP) and IL-5/eotaxin levels compared to the tissue samples obtained from Caucasians. Total IgE was elevated in allergic NPs compared with nonallergic NPs, but ECP levels were not increased. Thus, allergic disease likely has a negligible impact on ECP levels and eosinophil recruitment. Similar findings have been made in Caucasian polyps [14, 15, 69]. Of the Asian group, only two had asthma and nine were allergic patients. There was no difference between the allergic and nonallergic patients in relation to the eosinophilic infiltrate.

Despite the robust data on the distinct inflammatory and histomorphologic profiles observed in Western vs. Eastern NPs [70], there appears to be a noticeable "eosinophilic shift of CRSwNPs" based on emerging studies from Asia [65]. The rate of eosinophilic CRSwNPs increased by 27% within a 17-year-period in a South Korean cohort from a study conducted by Kim et al. [71]. Complementary to this finding was a study also conducted in South Korea, where Shin et al. found an increasing incidence of the eosinophilic type of CRSwNP in 2011 (62.6%), contrasted with 52.3% in 2001 and 47.7% in 2006 [72]. Another study performed in Thailand also noted a significant increase in the absolute eosinophil

count (from 5 to 35/hpf) and in IgE in tissue samples from 2011 compared to those from 1999 [73]. Wei et al. also found an increase in ECP/myeloperoxidase (MPO) in recurrent non-type 2 CRSwNP Chinese patients, suggesting that this particular endotype may evolve into type 2 CRSwNP with time [74]. Wang et al. in Beijing, China, also found that the proportion of eosinophilic CRSwNPs significantly increased from 59.1% to 73.7% over 11 years [75]. Although preliminary, these data allude to the influence of environmental factors on NP endotype, potentially through the westernization of diet, increased pollution, and antibiotic use. As a result of modernization of the global medical infrastructure, effects of reduced infections during childhood on the immunologic response have been proposed as the "hygiene hypothesis." It is hypothesized that changes in industrialized countries have led to a decreased burden of infections, which are associated with the rise of allergic and autoimmune diseases. It is possible that some of these effects play a role in the global differences in CRS prevalence and endotypes.

It is clear that variation in the physiology of NPs differs amongst Asians and Caucasians, yet there have been only limited investigations into other ethnic and racial backgrounds. A collaboration between three otolaryngology departments from various continents, Eritrea (Africa), China (Asia), and Switzerland (Europe), attempted to better characterize the racial variation of NPs [76]. In this report, the African and Chinese participants did not receive preoperative steroids or antibiotics, whereas the Caucasians were treated preoperatively with prednisolone 1 mg/kg/day for 5 days and trimethoprim/sulfamethoxazole for 10 days. Compared to Chinese and Caucasians, Africans presented with a more progressive disease in which NPs extended into the nasal cavity and were ulcerated. Eosinophil density was also greater in African polyps ($p < 0.001$) compared to Chinese and Caucasian NPs. There was no difference in the amount of eosinophils between Chinese and Caucasian NPs. Plasmocytes and lymphocytes were abundant in Chinese and Caucasian NPs and rare in African NPs. No difference was observed in the number of mast cells in any group. Unfortunately, the patients included in these analyses were not standardized in relation to preoperative treatment. The Caucasian cohort had been treated with preoperative steroids, which would likely suppress the presence of inflammatory mediators in the polyp biopsies. Both the Chinese and African cohorts received no preoperative treatment. The root cause of these discrepancies is likely due to the socioeconomic disparities among the study countries, resulting in a significant variation in the patients' access to health care and likely affecting the molecular data. Just as NPs of Caucasians and Asians can exhibit significant cellular and molecular differences, it is possible that polyps from African patients also show significant variation in the cellular and molecular profiles.

Take-Home Pearls

- An NP is a phenotypic manifestation of multiple possible immunologic processes.
- The significant association between NPs and asthma suggests a similar underlying pathophysiology that is independent of atopy.
- Although some CRSwNP cases are associated with established genetic syndromes, most patients likely have multiple, subtle, and as yet unknown genetic and epigenetic variations that combine with environmental factors, resulting in polyp formation.
- Further study is necessary to elucidate the key factors that account for the variability in polyp epidemiology.

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Phenotypes and Endotypes of Nasal Polyps in the Asian Population

Xiangdong Wang, Kun Du, and Luo Zhang

Core Messages

- CRSwNP with asthma comorbidity manifests as one phenotype with more severe severity of disease.
- The heterogeneity observed in different phenotypes of CRSwNP represents challenges for clinical treatment.
- Therefore, the classification of endotypes can assist in seeking tailored therapeutic options.
- Presently, endotyping CRSwNP based on the eosinophil (Eos) pattern is relatively easy to perform in clinical practice.
- In Asia, there are regional differences for the nature of the Eos profile.
- For instance, the eosinophilic nasal polyps were present in 33.3% and 46.4% of patients with CRSwNP in Korea in 2007 and in China in 2009, respectively.
- Furthermore, over the last 20 years, the data from several Asian countries reveals that the percentage of patients with eosinophilic nasal polyps has been increasing.
- There are some clinical measures that can help to preoperatively predict eosinophilic nasal polyps without the need to obtain polyps tissues, involving blood eosinophil count, computed tomography (CT) scores for the ethmoid sinus and maxillary sinus, and the combination of blood Eos percentage and olfaction scores.
- In future, inflammatory endotypes based on immune markers will guide the treatment with biologics such as monoclonal antibodies.

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and sinus that affects about 11% of adults in Europe [1], about 12% of adults in the United States [2], and 2.2% [3] or 8% [4] of adults in China. Generally, CRS was classified into two main phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [5]. Although the prevalence of CRSwNP in Europe is estimated to be 2.1–4.4% and is 4.2% in United States [6–8], it manifests greater disease severity than CRSsNP. Thus, ENT clinicians commonly pay more attention to the management of CRSwNP [5].

Nasal polyps in CRS are outgrowths of edematous inflammatory tissue that have grown into the middle meatus and sinuses. Heterogeneity in the pathology of nasal polyps influences clinical phenotypes, responses to treatment, and outcomes. As the upper and lower airways are considered as "united airways" [9], asthma is a common comorbidity of CRSwNP and occurs in up to 71% of patients with CRSwNP [10]. The phenotype of CRSwNP with asthma is more likely to manifest as severe disease and recur after sinus surgery [11].

The pathogenesis of CRSwNP is multifactorial and includes chronic inflammation, T and B lymphocytes, innate lymphoid cells (ILCs), inflammatory cells such as eosinophils (Eos) and neutrophils, and cytokines [12, 13]. Therefore, the phenotype of CRSwNP with or without asthma cannot fully represent this disease entity. To better

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reflect the inflammatory processes within NP tissues, endotypes of CRSwNP that employ inflammatory mediators and cytokines should play an important role. Endotypes are defined as subtypes of disease with unique pathomechanisms that provide additional information underlying the disease [14]. The classification of endotypes will guide progress in setting up diagnostic measures, understanding the development of the disease, evaluating prognosis and risk factors, and seeking tailored therapeutic options specifically for patients with severe disease.

1 Endotypes of CRSwNP Based on Inflammatory Cellular Patterns

Endotyping CRSwNP based on the percentage of Eos or the absolute Eos count in NP tissues is relatively easy to perform in clinical practice. Higher levels of Eos infiltration within mucosa tissues are associated with severe clinical manifestations and poor treatment outcomes [15, 16]. In this regard, many cohort studies have investigated the classification of eosinophilic CRSwNP (ECRSwNP) and noneosinophilic CRSwNP (non-ECRSwNP). However, these studies demonstrated a variety of endotypes due to different geographic locations. ECRSwNP is predominantly observed in Western populations and accounts for more than 80% of cases of nasal polyps, while less eosinophilic and more neutrophilic inflammation is observed in Asia [17–19]. Even in Asia, the endotypes of CRSwNP vary in different countries. For instance, two single-center studies showed that eosinophilic nasal polyps were present in 33.3% and 46.4% of patients with CRSwNP in Korea in 2007 [20] and in China in 2009 [21], respectively. Using cluster analysis, Lou et al. found Chinese CRSwNP patients may be classified into 5 clusters with presence of predominantly plasma cells (23.8%), lymphocytes (12.8%), neutrophils (7.7%), eosinophils (37.2%), or mixed inflammatory cells (18.6%) [22].

2 Eosinophilia Shift of Nasal Polyps in Asian Population

Over the last 20 years, the percentage of patients with ECRSwNP in Asia has been increasing [17]. In Korea, the percentage significantly increased in 2011 (62.6%) compared with that in 2001 (52.3%) and 2006 (47.7%) [23]. In another study investigating the Korean population over a 17-year period, the prevalence of eosinophilic polyps increased from 24.0% in 1993 to 50.9% in 2010 [18]. A longitudinal study from Thailand revealed a significant seven-fold increase in eosinophilic inflammation in 2011 compared to the values obtained in 1999 [24]. A similar eosinophilic shift was observed in China. An 11-year study demonstrated that the proportion of patients with ECRSwNP significantly increased from 59.1% to 73.7% in 2003–2005 and 2014–2016, respectively [25]. Another study reported that the proportion of patients with ECRSwNP was 15.7% from 2000 to 2001 and 44.0% from 2014 to 2015 [26]. A recent research also verified the eosinophilia shift in Northern China over past 2–3 decades [27].

3 Diagnostic Criteria of ECRSwNP and Non-ECRSwNP

According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020), a tissue Eos number of >10 per high-power field (HPF) in nasal polyps was recommend as a cutoff value of ECRSwNP [28]. Of note, the identification of ECRSwNP can be based on standard deviation of healthy controls [21], recurrence of nasal polyps [29], assessment of quality of life, asthma or allergy comorbidity [30], and so forth. Thus, classifying ECRSwNP is difficult and the definition of eosinophilic nasal polyps was inconsistent in different studies. To better classified ECRSwNP, reference intervals (RIs) and clinical decision limits (CDLs) have been considered [31]. RIs are defined as the interval between the two reference limits (2.5th and 97.5th percentiles) from a healthy population, which helps to distinguish patients from healthy subjects. By contrast, CDLs result from diagnostic tests that distinguish between two clinical subgroups [32]. In this context, the identification of ECRSwNP by recurrence of nasal polyps, assessment of quality of life, asthma or allergy comorbidity, that is related to CDLs, might be better at distinguishing ECRSwNP from non-ECRSwNP. According to Toro et al., recurrence was the most relevant parameter with a low risk of bias in the classification of ECRSwNP [33]. A tissue Eos proportion of >27% of total cells or a tissue Eos absolute count of >55 Eos/HPF may act as a reliable cutoff value, which showed balanced sensitivity and specificity for the prediction of nasal polyp recurrence [29]. Recently, this criteria was widely used to classify ECRSwNP [34, 35], and this cutoff value was further demonstrated in a meta-analysis [36].

Additionally, Cao et al. [21] recommended an Eos percentage of >10% of total inflammatory cells within nasal polyps as ECRSwNP. This cutoff value was identified through a comparison of the percentage of eosinophils in patients with CRSwNP and controls, which was related to RIs. When the percentage of eosinophils in polyp tissues exceeded twice the standard deviation (SD) of the mean of controls, the patients were diagnosed with ECRSwNP. Jeong et al. [30] used a cutoff value of 11% of the Eos percentage to identify ECRSwNP, in which patients with ECRSwNP

Table 1 Summary of the studies investigating the eosinophilic endotype of CRSwNP in the Asian population

Authors, publication year	Population	No. of samples	Definition of ECRSwNP	Proportion of ECRSwNP
Kim et al. [20], 2007	Korean	30	Percentage of Eos >5% of inflammatory cells	ECRSwNP = 33.3% Non-ECRSwNP = 66.7%
Cao et al. [21], 2009	Chinese	151	Percentage of Eos >10% of inflammatory cells	ECRSwNP = 46.4%
Jeong et al. [30], 2011	Korean	118	Percentage of Eos >11% of inflammatory cells	ECRSwNP = 62.7%
Kim et al. [18], 2013	Korean	104 (in 1993) 112 (in 2011)	Eos count >5 Eos/HPF	ECRSwNP in 1993 = 24% ECRSwNP in 2011 = 50.9%
Michael et al. [24], 2013	Thai	47 (in 1999) 42 (in 2011)	NA	Eosinophilic shift from 1999 to 2011
Shin et al. [23], 2014	Korean	107 (in 2001) 111 (in 2006) 131 (in 2011)	NA	Eosinophilic shift from 2001 to 2011
Lou et al. [29], 2015	Chinese (Beijing, northern China)	387	Percentage of Eos >27% of inflammatory cells or Eos count >5 Eos/HPF	ECRSwNP (Eos>27% of inflammatory cells) = 56.8% ECRSwNP (Eos>55/HPF) = 49.9%
Jiang et al. [26], 2019	Chinese (Central China)	108 (2000–2001) 134 (2014–2015)	Percentage of Eos >10% of inflammatory cells	ECRSwNP (2000–2001) = 15.7% ECRSwNP (2014–2015) = 44.0%
Wang et al. [25], 2019	Chinese (Beijing, northern China)	115 (2003–2005) 114 (2014–2016)	Percentage of Eos >10% of inflammatory cells	ECRSwNP (2000–2001) = 59.1% ECRSwNP (2014–2015) = 73.7%
Yu et al. [27], 2021	Chinese (Beijing, northern China)	150 (1993–1995) 150 (2015–2019)	Percentage of Eos ≥54.5% of inflammatory cells	ECRSwNP (1993–1995) = 9.3% ECRSwNP (2015–2019) = 32.0%

Abbreviations: *Eos* eosinophils, *ECRSwNP* eosinophilic chronic rhinosinusitis with nasal polyps, *HPF* high-power field, *NA* not available

had a significantly higher incidence of asthma and allergy than those with lower levels of tissue Eos in a Korean population. Additionally, there exist other criteria for ECRSwNP. For instance, nasal polyps might be defined as eosinophilic when the average eosinophil count is >5 eosinophils/high-power field (HPF) [18], eosinophils comprise more than 5% of the total inflammatory cells in nasal polyps [20], or eosinophil proportion ≥54.5% of the total inflammatory cells [27]. The detailed characteristics of CRSwNP in the Asian population and definition of ECRSwNP are presented in Table 1.

4 Prognosis of ECRSwNP/Non-ECRSwNP and Predictive Indicators

ECRSwNP and non-ECRSwNP have distinct clinical manifestations. For instance, corticosteroid treatment might have more efficacy in controlling the symptoms of patients with ECRSwNP but not non-ECRSwNP [37]. Patients with CRSwNP and less eosinophil infiltration are more likely to respond to macrolide treatment [38]. For patients who failed to gain control of the disease after appropriate medical treatment, sinus surgery is required. ECRSwNP has a strong tendency to recur after sinus surgery [39]. For example, the ECRSwNP subtype has highest recurrence rate of 98.5% [29]. In this context, for patients with severe type 2 inflammation, a reboot approach that aims to remove the inflamed mucosa from all sinuses can help reduce the postoperative recurrence rate [40]. Therefore, pre-operative and clinical prediction of ECRSwNP can help provide evidence for treatment options. Presently, histological criteria are the gold standard for classification of eosinophilic and non-ECRSwNP.

However, it is not practical to perform histological analysis before surgery or evaluate patients who do not undergo sinus surgery. Therefore, several studies have attempted to find simple classification methods that are applicable in clinical practice. Hu et al. [41] found that an absolute blood Eos count >0.215 × 10^9/L yielded a sensitivity of 74.2% and a specificity of 86.5% for the diagnosis of ECRSwNP. Meng et al. [42] reported that the ratio of computed tomography (CT) scores for the ethmoid sinus and maxillary sinus (E/M ratio) had an optimal accuracy to predict ECRSwNP, with an E/M ratio cutoff point of >2.59 that demonstrated a sensitivity of 94.2% and a specificity of 89.6%. Recently, Xu et al. [43] combined cutoff values of 3.85% for blood Eos percentage and 3% for olfaction scores to differentiate ECRSwNP from non-ECRSwNP, which showed a sensitivity of 75.5% and specificity of 78.0%. Collectively, blood Eos, olfaction, and CT scores for the E/M ratio are currently useful clinical markers to predict ECRSwNP. On the other hand, She et al. reported the potential value of nasal cytology by use of nasal brushings processed by a liquid-based cytological technique [44]. Meanwhile, E/M ratio of CT scores [45], combination of asthma history, percentage of blood Eos, concentration of

serum total IgE and previous surgery [46], as well as Charcot-Leyden crystal (CLC) protein in nasal secretions [47] have been reported to predict CRSwNP recurrence.

5 Endotypes of CRSwNP Based on Profiles of Key Cytokines

The dichotomy of ECRSwNP and non-ECRSwNP is not able to encompass the molecular diversity of patients with CRSwNP. Additionally, neutrophils might be present and activated in each eosinophilic polyp tissue, which is reflected by biomarkers corresponding to neutrophilic inflammation [48, 49]. To adequately identify the immunologic profiles of the disease, endotyping the disease by quantifiably employing inflammatory mediators and cytokines should be better. CRSwNP and CRSsNP are two phenotypes of CRS, which is considered to be a disease entity. Thus, relevant studies usually investigate the endotypes of CRS, simultaneously including CRSwNP and CRSsNP.

Tomassen et al. [48] sought to identify inflammatory endotypes based on immune markers in the nasal mucosa tissues from 11 countries in Europe. In that multicenter study, nasal tissues from 173 patients with CRS and 89 controls undergoing surgery were collected. The underlying markers within tissues, such as T-helper cell (Th) cytokines IL-5, IFN-γ, IL-17A, TNF-α, IL-22; pro-inflammatory cytokines IL-1β, IL-6, and IL-8; granulocyte activation markers eosinophil cationic protein (ECP) and myeloperoxidase; remodeling factors TGF-β1 and albumin; and total IgE and staphylococcus aureus enterotoxin specific IgE (SE-IgE), were analyzed. The patients were classified in 10 clusters by cluster analysis. Four clusters showed non-type 2 inflammation, of which 3 clusters demonstrated limited inflammation with a type 1, type 17, or type 22 profile. These patients with non-type 2 inflamed nasal mucosa predominantly had a CRSsNP phenotype. The other 6 clusters showed moderate to high levels of IL-5, ECP, and IgE. Among the 6 clusters, 3 clusters showed moderate IL-5 concentrations and a moderately increased prevalence of CRSwNP and comorbid asthma. In the other 3 clusters with high IL-5 levels, patients almost exclusively had the CRSwNP phenotype, among whom a strongly increased asthma prevalence was observed. Two clusters showed the highest levels of IgE and asthma prevalence with all samples expressing SE-IgE. According to this study, CRS can be differentiated in non-type 2 (44%), moderate (38%), and severe type 2 (18%) inflammation, with a clear increase in the nasal polyp phenotype (from less than 15% to more than 90%) and comorbid asthma from approximately 5% to 60–70%.

Turner et al. [50] investigated inflammatory CRS endotypes in a North American population based on the collection of sinonasal mucosa from 90 patients with CRS. Through assay of 18 inflammatory mediators that reflect Th1/Th2/Th17-associated inflammation, the patients were divided into 6 clusters. Cluster 3 and cluster 4 were both exclusively composed of patients with CRSwNP and had the highest levels of comorbid asthma at 83% and 86%, respectively. Cluster 3 was defined by high levels of IL-5, IL-6, IL-9, IL-10, IL-13, IL-17A, IFN-γ, and eotaxin, and cluster 4 had elevated levels of IL-5, IL-9, and IL-13. In contrast, cluster 4 additionally was distinguished by elevated IL-2, IL-3, and IL-4 and was noted to have higher levels of IL-17A than cluster 3. This finding demonstrates that even in patients with a similar phonotype of CRSwNP and comorbid asthma, the disease manifests as a heterogeneous inflammatory process. Additionally, the inflammatory mechanism underlying nasal polyps did not correspond to a distinct Th1-, Th2-, or Th17-associated signature.

Recently, Wang et al. [51] performed a cluster analysis of 16 inflammatory and remodeling factors in nasal mucosal tissues from 128 patients with CRS and 24 control subjects in Chinese population. Patients were classified into 5 clusters. Clusters 1 and 2 were defined as non-type 2 inflammation with a higher expression of IL-19 in cluster 1 and IL-27 in cluster 2. Cluster 3 showed low type 2 inflammation (low IL-5 and ECP) and the highest levels of pro-inflammatory, neutrophil, and remodeling factors. Cluster 4 manifested a moderate type 2 inflammation (moderate IL-5, ECP, and total IgE). Cluster 5 had a high type 2 inflammation (high IL-5, ECP, and total IgE) with moderate expression of neutrophilic factors (such as IL-8, IL-6, and TNF-α). The proportion of CRS with nasal polyps, asthma, allergies, anosmia, aspirin sensitivity, and the recurrence of CRS increased from Clusters 1 to 5. This study investigated the endotypes of CRSwNP in Chinese population. Similar with the results from European and American populations, it confirms that a higher risk of asthma comorbidity and recurrence is associated with a higher type 2 inflammation.

In Europe, more than 80% of nasal polyps are characterized by type 2 inflammation, whereas in Asia, less frequent and severe type 2 immune reactions have been found [15, 52, 53]. Wang et al. [52] investigated IL-5 expression in CRS tissue obtained from 3 continents. Approximately 15% to 18% and 15% to 27% of CRSwNPs showed undetectable IL-5 in the European center and Oceanian center, respectively, whereas the proportion varied from 39% to 80% in the Asian center. With regard to Th1-, Th2-, and Th17-associated cytokines (IFN-γ, IL-5 and IL-17), approximately 39% of patients in Japan and 16% and 19% of patients in Beijing and Chengdu, China, respectively, showed exclusive IL-5 expression. This finding demonstrates more frequent type 2 inflammation-induced nasal polyps in Japan than in China. The other two studies also evaluated the endotypes of CRS in Chinese population. Wei et al. [53] found 4 clusters of patients with CRSwNP in Chengdu, and the proportion of

type 2 endotype (higher levels of IL-5, IgE, ECP, and highest positivity of SE-IgE) was only 15.9% but with 72.7% of recurrence. Liao et al. [15] identified 7 clusters of patients with CRSwNP and CRSsNP in central region of China and 13.01% of typical type 2 endotype among all patients.

In summary, CRSwNP predominantly manifests as moderate and severe type 2 endotypes, which are caused by ILC2, T-helper cell type 2 (Th2)-biased responses, eosinophilia, and IgE synthesis [54, 55]. Compared with western populations, Asian populations demonstrate less frequent and lower degrees of type 2 inflammation. The dichotomy of eosinophilic and noneosinophilic inflammation can be widely used in clinical practice. According to this classification, more appropriate treatment might be selected prior to medical administration to benefit patients. Furthermore, a method of clustering distinct CRS immunological endotypes largely correlated with different phenotypes. In the future, for patients with difficult-to-treat CRSwNP, targeted treatment for key biomarkers involved in different endotypes should be used to treat patients with severe disease.

Take-Home Pearls

- Asian patients demonstrate less frequent and lower degrees of type 2 inflammation as compared with western populations.
- However, there exists an eosinophilic shift in Asian populations over the last 20 years.
- An Eos percentage of >27% of total inflammatory cells or an absolute count of >55 Eos/HPF within nasal polyps is a reliable diagnostic criterion for eosinophilic nasal polyps.
- Presently, using this criteria, computed tomography (CT) scores for the ethmoid sinus and maxillary sinus (E/M ratio) had an optimal accuracy to predict eosinophilic nasal polyps, with an E/M ratio cutoff point of >2.59 that demonstrated a sensitivity of 94.2% and a specificity of 89.6%.

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Pathology of Nasal Polyps

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Core Messages

- The most common polyps found in the nose and paranasal sinuses are those associated with chronic rhinosinusitis (CRS), known as CRS with nasal polyps (CRSwNPs).
- CRSwNPs represent a group of diseases with a diverse range of etiologies and inflammatory pathways. Histological subclassification of CRSwNPs is mainly descriptive and is not specific to a particular clinical entity or etiology.
- The presence of eosinophilic mucus should not be ignored, since this is an important diagnostic criteria for the clinical subcategories of CRSwNPs, namely, eosinophilic mucus chronic rhinosinusitis (EMCRS) and allergic fungal rhinosinusitis (AFRS).
- A histopathological reporting template addressing the key histopathological entities in CRSwNPs can facilitate clinical and research outcomes.
- Unilateral or unusual-appearing polyps require further investigations to exclude vascular pathology and a biopsy to exclude neoplastic and malignant lesions.
- Pathologies that present as polypoid masses include benign conditions (sinonasal papillomas, hamartomas, angiofibromas) and malignancies (carcinomas, lymphomas, melanoma, and mesenchymal neoplasms).

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1 Introduction

The term "polyp" refers to the macroscopic appearance of a pedicled tissue arising from a mucosal surface and projecting into a lumen or cavity. The histopathology of polyp tissue affecting the nose and paranasal sinuses is diverse, ranging from inflammatory nasal polyps to benign and malignant epithelial, mesenchymal, and hematolymphoid neoplasms (Table 1). In the context of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNPs), "polyps" refer to benign inflammatory tissue projections with an epithelial lining within the sinonasal cavity. There are several histopathological features that differentiate CRSwNPs from other types of polypoid lesions occurring in the nose and paranasal sinuses. Furthermore, CRS nasal polyps may have some unique characteristics that are distinguishable from the surrounding non-polypoid CRS mucosa.

1.1 Normal Sinonasal Histology

Normal sinonasal histology is characterized by both structural components, including the epithelium, basement membrane, and submucosal tissue, and nonstructural components, including resident and nonresident cells from the lymphoid and myeloid lineages.

1.1.1 Structural Components

The Epithelium and Basement Membrane The anterior 2 cm of the nasal cavity is lined by skin, composed of an epidermis with a keratinizing stratified squamous epithelium, a fibrocollagenous dermis, and adnexal glands. The rest of the nasal cavity is lined by a respiratory-type mucosa that is derived from ectoderm, also known as the Schneiderian membrane. A normal sinonasal mucosa is depicted in Fig. 1. The respiratory epithelium consists of four major cell types: ciliated columnar or cuboidal cells, interspersed goblet cells,

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