Nasal Polyps in Cystic Fibrosis

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Core Messages

- Nasal polyps are common in cystic fibrosis (CF).
- Nasal polyps in children should prompt appropriate investigations for the potential diagnosis of CF.
- Possible etiologies for nasal polyp formation in CF include direct consequence of ΔF508 affecting chromosome 7, colonization with microorganisms including *Pseudomonas aeroginosa* and fungi, and IgE-mediated inflammation.
- Neutrophils are more common in polyps from CF patients compared with non-CF nasal polyposis.
- Conservative management with nasal irrigations and nasal steroids constitute first-line treatment.
- Surgical management of persistent and symptomatic polyps may also improve lung function, and consequently, quality of life.
- Simple polypectomy has a high rate of early recurrence, and thus, surgery should include at a minimum uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy.
- Topical delivery of novel medications may reduce the need for surgery.

17.1 Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disorder affecting the exocrine glands and is characterized by thick, viscous secretions in multiple organ systems, including the sinuses, upper and lower airways, gastrointestinal system, skin, and reproductive system. It has a high incidence in the Caucasian population, affecting 1 per 2,500 live births in the United States [14]. Chronic rhinosinusitis (CRS) and nasal polyps are not uncommon in CF patients. In addition to the morbidity due to the polypoid CRS, it is suggested that the extent of sinus disease may influence the severity of pulmonary disease [16]. The purpose of this chapter is to review the clinical spectrum of sinonasal disease in CF and management issues, especially in those undergoing pulmonary transplantation.

17.2 Epidemiology of Sinonasal Disease in Cystic Fibrosis

The frequency of nasal polyposis in CF ranges from 31 to 56% [6, 12, 22, 26, 39]. Polyps are most commonly reported in children aged 5–14 years; however, they can also develop in older patients [2, 22]. Males and females are equally affected [6, 12, 26, 39]. Polyps usually occur bilaterally [44], but have been reported unilaterally in up to 38% [6] (Fig. 17.1).

17.3 Etiology

17.3.1 Genetics

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

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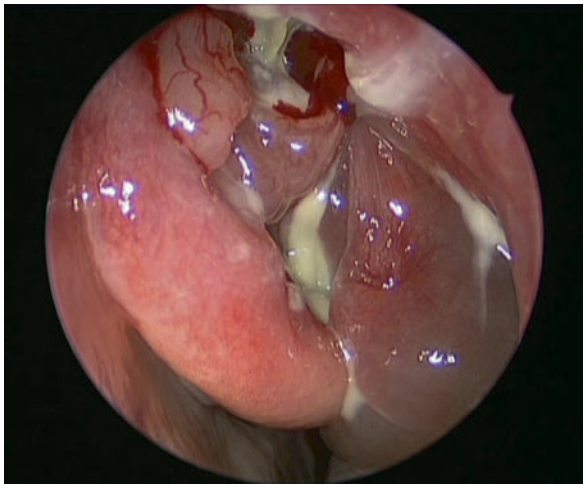

Fig. 17.1 Intraoperative view of left nasal cavity in child with CF showing polyps and mucopurulence in middle meatus

situated in region 31 on the long arm of chromosome 7 (7q31). This gene codes for a protein that functions as a cAMP-regulated chloride channel. Abnormal function of this channel results in abnormal sodium and chloride transport across the apical membrane of epithelial cells [45]. More than 1,000 mutations have been identified in the CFTR gene; however, the most common mutation, present in 70% of patients, is a deletion, designated ΔF508 mutation, which results in the loss of the amino acid phenylalanine at the 508th position. The most frequent genotype in CF is ΔF508/ΔF508 (i.e., ΔF508 homozygosity), followed by ΔF508 heterozygosity [28].

The genotype may influence the incidence of nasal polyposis in CF. Kingdom reported that CF patients with nasal polyposis undergoing surgery had a higher incidence of ΔF508/ΔF508 or ΔF508/G551D genotypes than those with CF and no nasal polyps [29]. Some found that ΔF508 homozygosity correlates with the presence of nasal polyps [26, 39]; however, others have not found otherwise [2, 6, 12, 22]. Interestingly, Kostuch reported a significantly higher incidence of ΔF508 heterozygosity in non-CF patients with nasal polyps (11.4%), compared to control subjects without polyps (1.4%) [31]. Thus, while the specific CFTR mutation may be connected with the development of nasal polyposis, it is likely that other factors also play an important role [6].

17.3.2 Pseudomonas Colonization

A significantly higher incidence of colonization with *Pseudomonas aeroginosa* is reported in CF patients with nasal polyps compared to CF patients without polyps [6, 22, 29]. *Pseudomonas* species produce several toxins, including hemolyzin and pyocyanin, a phenazine derivative. Pyocyanin has been shown to slow ciliary beat frequency and cause ciliostasis and epithelial disruption in vitro and, thus, may play a role in the pathophysiological events leading to the formation of nasal polyps [46].

17.3.3 Allergy

The role of allergy in the pathophysiology of nasal polyps in CF is unclear. The overall prevalence of atopy in CF does not appear to be different between polyp and nonpolyp patients [19, 22]. However, studies have shown that patients with positive skin prick tests are more likely to be colonized by *Pseudomonas species*, and this may be in fact responsible for the formation of polyps. Interestingly, a higher incidence of allergy to *Aspergillus fumigatus* in CF nasal polyps has been reported and allergic bronchopulmonary aspergillosis is known to affect 2–15% of patients with CF [42]. Thus, it is interesting to speculate whether fungi and allergy to fungi may have a role in causing nasal polyposis in these patients. Wise reported one third of fungal cultures to be positive among a series of 30 patients with CF, with two patients in their series being newly diagnosed with allergic fungal sinusitis [47]. Thus, allergic fungal sinusitis may be associated with nasal polyps in a subset of patients with CF; however, further studies are required.

17.4 Pathology

There are several important differences in histological characteristics of polyps from CF and non-CF patients. Polyps in non-CF patients are characterized by eosinophil infiltration, while those in CF are characterized by predominantly neutrophil infiltration [24, 38]. Eosinophils are seen in CF polyps; however, the numbers of these are significantly fewer than seen in non-CF polyps [24, 38]. The basement membrane of polyps is thinner and more delicate, the mucous glands mainly contain acid mucin, and submucosal hyalinization is absent. In contrast, non-CF polyps typically

have a thick basement membrane and contain mucous glands with neutral mucin [17].

CF polyps typically contain cytokines associated with a T helper 1 (T_H1) inflammatory response [43]. Neutrophil populations, levels of IL-8, and myeloperoxidase (MPO) are significantly higher, whereas levels of IL-5, eotaxin, ECP, and IgE are significantly lower in CF polyps compared with non-CF polyps. Proteins such as human β-defensins 2 (HBD 2) and toll-like receptor 2 (TLR-2) [8] and surfactant proteins A and D [43] are also increased. These may be a consequence of predisposition to recurrent infections due to dysfunctional CFTR in the nasal epithelium that causes impaired chloride transport, which changes the physiochemical properties of nasal mucus, resulting in thick and viscous mucus. Increased levels of interleukin-9 and upregulation of the calcium-activated chloride channel, hCLCA1, may contribute to mucus overproduction by upregulating the expression of soluble gel-forming mucins [21]. The viscosity of the mucus blanket is further increased by DNA macromolecules from degenerating neutrophils [7]. The increased viscosity of nasal mucus contributes to decreased effectiveness of the mucociliary transport, and consequently, increased the risk of infection and inflammation. The increased viscoelastic properties of mucus may also contribute to mechanical obstruction of sinus ostia and air spaces causing impaired gas exchange and mucosal edema that further decreases ciliary function and enhances bacterial colonization. Bacterial products such as pyocyanin and hemolysin from *P. aeruginosa* may further impair mucociliary function. Thus, a vicious cycle of impaired mucociliary function, sinus ostial obstruction, and bacterial infection is created. Furthermore, it is also postulated that chronic infection with *P. aeruginosa* and *Staphylococcus aureus* may cause upregulation of innate defensive proteins TLR-2 and HBD 2, leading to a dysregulated neutrophilic inflammation [8]. Neutrophil elastase is known to cause mucosal damage and may thus prolong mucosal inflammation and contribute to edema and polyp formation [38].

In postlung-transplant patients with nasal polyposis, consideration should be given to the possibility of posttransplant lymphoproliferative disorder (PTLD). PTLD is an uncontrolled lymphoproliferation in the setting of pharmacological immunosuppression, usually caused by unrestrained stimulation of B-lymphocytes by Epstein–Barr virus (EBV). Although PTLD affecting the head and neck usually occurs in the setting of disseminated disease, isolated sinonasal PTLD is not uncommon, and in many cases, is only diagnosed after "incidental" nasal polypectomy [23].

17.5 Clinical Presentation

Nasal obstruction is the most common presenting symptom of nasal polyposis in CF; however, not all patients with polyps complain of nasal obstruction. It is likely that nasal obstruction in these patients is so long-standing that most patients have adapted to it. Rhinorrhea is also common, particularly among younger children, while older children may also complain of headache.

Whenever possible, children with CF should undergo nasal endoscopy to definitively ascertain whether or not polyps are present. This may be difficult in younger children owing to the lack of cooperation. Nasal endoscopy will commonly reveal polyps arising in the middle meatus, with the middle turbinate thinned and pushed medially against the nasal septum. Nasal polyps are rare in children who do not have CF. Thus, children with nasal polyps should initially undergo a sweat test. A sweat chloride level of greater than 60 mEq/L is considered diagnostic of CF, and this should be followed up with genetic testing and counseling.

17.6 Investigations

17.6.1 Radiology

Sinus radiographs are of limited application and computed tomography (CT) of the sinuses is now the investigation of choice. Common sinus CT scan findings include frontal sinus hypoplasia, maxillary sinus expansion with medialization, or even loss of the medial maxillary wall and mucocele or pseudomucocele of the maxillary sinuses (Fig. 17.2). Frontal sinus hypoplasia is thought to result from diminished postnatal growth as a result of chronic inflammatory disease

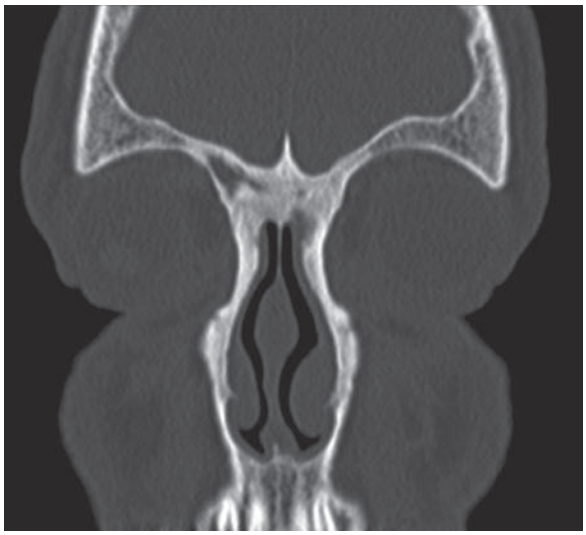

Fig. 17.2 Computed tomography scan of patient with CF showing hypoplastic frontal sinuses

and decreased sinus ventilation. A similar phenomenon may also be observed in the sphenoid sinuses. Of note, a significantly higher incidence of sinus hypoplasia has been reported in patients who are homozygous for the ΔF508 mutation [48]. The maxillary sinus findings are thought to result from the entrapment of thick inspissated mucus and polyp formation in the middle meatus. Like polyps, mucoceles are extremely rare in children and should suggest a diagnosis of CF. Magnetic resonance imaging (MRI) can differentiate between infectious material and thickened mucosa and thus complement CT scan findings [15].

17.6.2 Microbiology

Ideally, endoscopically guided bacteriological cultures should be obtained to guide antibiotic therapy, especially given the high levels of antibiotic resistance in CF; however, this may not be always possible in children. The most common bacteria found in CF sinusitis are *P. aeruginosa* and *S. aureus*. Of note, CF patients with polyps have been reported to show a significantly higher incidence of sinonasal *Pseudomonas* sp. infection compared to those without polyps [6, 22, 29]. Consequently, biofilm formation may be increased in CF compared to non-CF CRS patients [20].

17.7 Management

17.7.1 Medical

Medical treatment is the initial treatment step in the management of CF with CRS with and without polyps. Saline irrigation helps with clearing thick inspissated secretions, crusts, and proinflammatory mediators. Intranasal corticosteroids may also be effective in reducing CF polyp size [18]. Of note, children with CF who are commenced on systemic corticosteroids for pulmonary disease may also report improvement of their nasal symptoms. Systemic antibiotics are indicated where purulent secretions are present in the symptomatic patient and were possible, should be culture-directed, and where possible, should be culture-directed. The major target of antibiotic therapy is typically *P. aeruginosa*. Topical antibiotics have also been used and are being investigated. Nebulized tobramycin is used to treat endobronchial *Pseudomonas* where delivery of a high concentration enhances bactericidal activity while minimizing the risk of ototoxicity and nephrotoxicity. Moss and King found that the requirement for sinus surgery was reduced in CF patients who underwent serial sinus antimicrobial lavage in the postoperative period [35]. However, there are little data on the use of topical antibiotics beyond the perioperative period and on the long-term beneficial effects. Tobramycin may be administered as a 20 mg/mL solution and adverse effects at this concentration are not reported [13]. While topical tobramycin lavage is shown to reduce local bacterial counts in experimental animals, there is little evidence for eliminating biofilms [1, 4]. Recently, topical baby shampoo lavage has shown to be effective in removing bacterial biofilms in postsurgical patients and may have a role in select patients[5] (see below).

17.7.2 Surgery

Generally, surgery is indicated where medical measures fail to achieve adequate control of sinonasal disease. Following are the main issues of surgery in CF patients: (1) safety of the surgery; (2) impact of the surgery on nasal symptoms and quality of life; and (3) impact of surgery on pulmonary function. Major concerns relating to safety involve the risk of bleeding,

particularly where coagulation is abnormal due to vitamin K malabsorption and in the posttransplant patients, due to immune-suppressive therapy. Thus, consideration should be given to optimizing preoperative coagulation status in order to minimize bleeding and risk of complications [10]. Measures to reduce bleeding include preoperative oral corticosteroids and antibiotics. Surgery when performed by experienced surgeons, in close cooperation with experienced anesthesiologists and pulmonologists, there is good evidence that it may be performed safely [27, 40].

The second issue relates to whether or not surgery improves symptoms and quality of life in CF patients. Although there are little data regarding validated quality of life measures, many authors have reported significant improvement in sinonasal symptoms after surgery. Nasal obstruction is the most commonly improved symptom. Significant improvements in rhinorrhea and total rhinosinusitis symptom scores are also reported. Although headache is least likely to improve following surgery, its presence postoperatively may indicate recurrence of frontoethmoidal mucoceles [27, 44]. The third issue relates to the effect of surgery on pulmonary function and is controversial. There are conflicting reports on postoperative lung function, with temporary improvement shown by some [25, 41, 44] and no significant change by others [34, 37]. A significant decrease in the number of hospitalizations and mean number of intravenous antibiotic courses is also shown [41, 44].

17.7.2.1 Extent of Surgery

Surgical treatment includes simple nasal polypectomy and completely opening up the involved sinuses including maxillary, ethmoid, frontal, and sphenoid sinuses. The major drawback of simple polypectomy is shorter time to polyp recurrence [3, 44]. Although previous studies showed better long-term results in patients who underwent a "combined approach," including a Caldwell–Luc operation [3, 9], recent endoscopic studies have not shown a significant long-term beneficial outcome regardless of the extent of surgery [2]. We recommend that surgery in CF patients should include at least an uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy. In most cases, the uncinate process will already be thinned and medially displaced, and in many cases, a pseudomucocele may be present within the maxillary sinus. Uncinectomy and removal of polyps will allow this pseudomucocele to drain and a large middle meatal antrostomy can be achieved endoscopically without the need for a Caldwell–Luc operation [41]. Anterior ethmoidectomy is also often required, whereas posterior ethmoidectomy and sphenoidotomy need only be performed when there is radiologic or endoscopic evidence of disease in these sinuses. As the frontal sinuses are generally underdeveloped, routine exploration of the frontal recess is unnecessary, but should be performed when disease is present in that location. We do not routinely resect the caudal middle turbinate; however, this may be performed as advocated by others [44].

Nasal polyp recurrence after surgery is common and reported in 13–89% of patients [2, 3, 49], depending on the length of follow-up and definition of recurrence. The extent of disease as indicated by Lund–Mackay scores from the preoperative CT scan has been reported to be a predictor of the risk of requiring further surgery in CF [2]. Importantly, even though polyps may recur in up to 32% of patients, the extent of polyps may be significantly better in the preoperative state [27, 44]. The median time interval to repeat surgery is approximately 4 years [49], thus studies with follow-up periods of less than this may not accurately report recurrence rates.

17.7.3 Novel Treatments

17.7.3.1 Dornase Alfa

Large amounts of DNA from degenerating neutrophils in CF are important contributors to the high viscosity of nasal secretions. Dornase alfa (recombinant human deoxyribonuclease) cleaves extracellular DNA and is shown to reduce sputum viscosity and improve lung function in CF (36). Intranasal use of dornase alfa postoperatively is shown in a randomized double blind trial to improve symptoms and endoscopic scores in CF patients compared to placebo treatment [7].

17.7.3.2 Ibuprofen

Upregulation of cyclooxygenase (COX) enzymes 1 (COX-1) and 2 (COX-2) has been reported in the nasal

polyps of patients with CF [36]. High-dose ibuprofen therapy can slow the decline in lung function in children with CF [30]. Recently, high-dose ibuprofen therapy has also been found to reduce the size of polyps in CF children [33]. Further data are awaited from controlled studies.

17.7.3.3 Antibiofilm Therapies

Pseudomonas biofilm formation in CF patients may be a significant contributor to sinonasal inflammation. Novel medications such as quorum sensing blockers and other antibiofilm therapies may contribute to our future management. Detergents, such as baby shampoo, have been reported to possess antibiofilm forming properties when used in irrigations at 1% [5].

17.7.4 Management of Nasal Polyps Prior to Lung Transplantation

Management of sinonasal disease is an important consideration in CF patients before and after lung transplant. *P. aeruginosa* infections are a serious consideration in postlung transplant patients, and the nose and paranasal sinuses are considered to be the reservoir for these infections [17]. Thus, several authors have described protocols that involve endoscopic sinus surgery, followed by various regimes of intrasinus tobramycin prior to transplant [11, 32]. It is unclear if such regimes improve outcomes or not.

17.8 Conclusion

Nasal polyps are common in children and adults with CF. Initial treatment in most patients consists of management with nasal irrigations and topical steroids; however, the treatment of large or persistent polyps may eventually require surgery to improve nasal airway and quality of life. When performed by an experienced endoscopic surgeon in conjunction with anesthesiologists and pulmonologists familiar with CF patients, surgery should be a safe undertaking. Further advances in our understanding of the pathophysiology of polyps in CF may allow the development of newer medical treatments, which may further improve patient outcomes.

Take Home Pearls

- Conservative management with nasal irrigations and topical steroids constitutes the first-line management of nasal polyposis in CF.
- When surgery is performed, at a minimum this should entail nasal polypectomy, uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy. There is no known benefit to performing more extensive surgery in the absence of radiological evidence of inflammation in the posterior ethmoids, sphenoid, or frontal sinuses; however, if these areas are diseased, they should also be addressed at the time of surgery.
- Adequate postoperative medical therapy is essential to prevent early recurrence of nasal polyps or rhinosinusitis. In the future, improvements in our understanding of the pathophysiology of polyps in CF may allow for the development of new treatments, which may improve patient outcomes.

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