Chapter 16
The Role of Reflux Disease in Chronic Rhinosinusitis

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Introduction

Chronic rhinosinusitis (CRS), an inflammatory disease of the paranasal sinuses, is one of the most commonly encountered diseases worldwide, rivaling asthma and diabetes mellitus in prevalence [1]. Affecting an estimated 1% to 12% of the world population, CRS is associated with impaired quality of life and marked functional limitations owing to the disease's symptom profile and chronicity [2]. By definition, CRS persists for at least 12 weeks and is characterized by nasal mucopurulent drainage, nasal obstruction or congestion, facial pain, pressure or fullness, and decreased or loss of sense of smell. Due to the costs of diagnostic tests, medical and surgical treatments, and lost work productivity, a significant socioeconomic burden is incurred with annual direct and indirect costs for CRS estimated at $12.8 billion in the United States [3].

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Pathophysiology

The pathophysiology of CRS involves inflammatory changes in the nasal and sinus mucosa, leading to mucosal edema, ostial obstruction, mucosal stasis, and subsequent infection. As a multifactorial disease, many predisposing factors operating alone or in combination have been recognized to initiate these inflammatory events, including viral, bacterial, and fungal infections, inhalation of allergens and environmental pollutants, and anatomic etiologies [4, 5].

Gastroesophageal reflux has been associated with numerous supraesophageal symptoms, under the title of laryngopharyngeal reflux (LPR) disease, and implicated in the pathogenesis of various disease processes in the head and neck, including dysphonia, benign vocal cord lesions, laryngospasm, subglottic stenosis, and rhinosinusitis [4, 5]. The relationship between the gastrointestinal tract and CRS was established when Holmes et al. in 1950 proposed a connection between sinonasal disease and gastric hypersecretion [6]. A high prevalence of LPR, also known as extraesophageal reflux (EER), in CRS patients has been reported in the literature; however, no definitive causal association has been established [5, 7–10]. The role of LPR as a potential exacerbating factor of upper airway inflammatory disease has only recently been appreciated.

Mechanisms: LPR and CRS

Although the mechanism in which LPR may contribute to CRS remains elusive, three theories have been suggested. The first of these proposes that the direct exposure of the nasopharynx and nasal cavity to the refluxate causes mucosal inflammation and impaired mucociliary clearance, thereby resulting in sinus ostial obstruction and increased incidence of infection. Alterations in pH have been shown to affect ciliary motility and morphology in respiratory mucosa [11]. In children, nasopharyngeal reflux has been demonstrated in CRS patients using 24-hour pH probe studies [12, 13]. Phipps et al. in 2000 reported that 63% of their pediatric cohort with CRS had evidence of LPR, which exceeds the prevalence of 5% observed in a normal healthy population [13]. Ozmen et al. in 2008 similarly found a higher incidence of pharyngeal acid reflux events in patients with CRS (88%) compared to control (55%). The study also demonstrated the presence of pepsin in nasal lavage fluid, providing direct evidence of gastric content reflux into the nasopharynx, in 82% of patients in the study group compared to 52% in the control group. A statistically significant correlation between the number of LPR events and pepsin-specific activity was found [4]. Furthermore, anti-reflux therapy has been observed to dramatically reduce the number of pediatric patients with CRS requiring sinus surgery [14].

A second possible mechanism involves a vagus nerve-mediated inflammatory response, in which autonomic nervous system dysfunction leads to sinonasal edema and inflammation with subsequent ostial obstruction. This phenomenon has been

described in asthmatics with gastroesophageal reflux disease (GERD), where a hypervagal response may contribute to the heightened airway responsiveness secondary to esophageal acidification. Vagolytic doses of intravenous atropine have been demonstrated to partially ablate the bronchoconstrictive response to acid reflux, supporting the role of a vagally mediated reflex in the inflammatory process [15]. To investigate whether an esophageal-nasal reflex exists, Wong et al. infused normal saline and hydrochloric acid into the lower esophagus of ten healthy volunteers without GERD or sinonasal disease and analyzed nasal symptom scores, nasal inspiratory peak flow, and nasal mucus production following the esophageal challenge. The study found increased nasal mucus production, increased nasal symptom scores, and reduced peak nasal inspiratory flow after normal saline and hydrochloric acid infusion, with return to baseline within 45 minutes. The authors concluded that these results support the possibility that a neural reflex mediated by the vagus nerve exists between the esophagus and the paranasal sinuses and that this neuropathic inflammation may facilitate the development of CRS in patients with GERD [16].

A third possible mechanism implicates *Helicobacter pylori* as the facilitator of CRS in the context of reflux disease. *H. pylori*, a Gram-negative, microaerophilic bacterium known to cause stomach ulcers and gastritis, has been detected in sinonasal mucosal biopsy specimens by polymerase chain reaction in CRS patients across multiple studies. Ozdek et al. reported that *H. pylori* DNA was detected in 4 of 12 patients with CRS, whereas it was not detected in any patients without CRS. Gastroesophageal reflux-related complaints were noted in 3 of 4 patients with positive results for the bacterium [17]. Morinaka et al. observed that *H. pylori* was detected in 3 of 19 nasal and maxillary sinus specimens collected from CRS patients. However, whether *H. pylori* is a causative agent for CRS remains unknown [18] (Figs. 16.1 and 16.2).

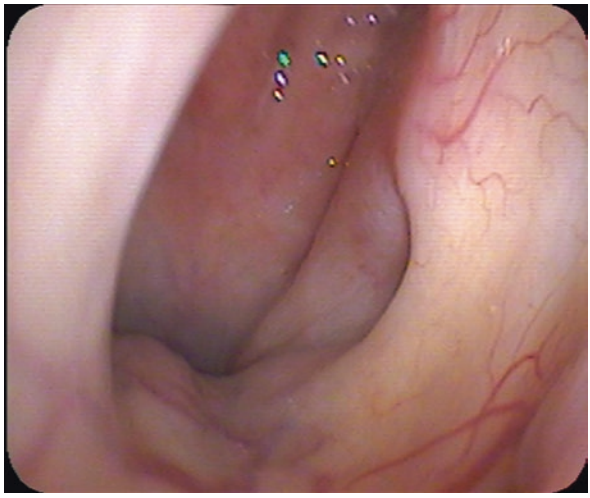

Fig. 16.1 Nasal endoscopy with view of normal Eustachian tube and sinus mucosa

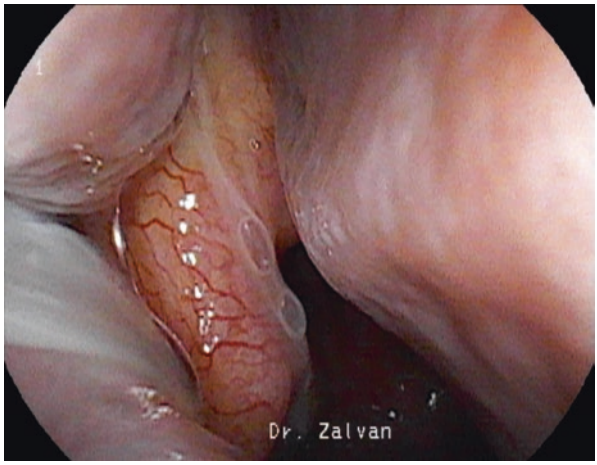

Fig. 16.2 Nasal endoscopy of acute sinusitis in setting of chronic, recurrent sinusitis with purulent drainage from the maxillary and sphenoethmoid sinuses into the nasopharynx

Management and Treatment Failure

The medical management of CRS encompasses a prolonged course of antibiotics targeting the upper respiratory flora, saline irrigation, and nasal and oral corticosteroids. Endoscopic sinus surgery (ESS) is the preferred treatment for patients with CRS who remain symptomatic despite maximal medical therapy [5]. While ESS has been shown to be an effective therapeutic option, with long-term symptomatic improvement in 98% of patients, many factors have been associated with its failure, including irreversible mucosal disease, allergy, tobacco use, and GERD [5, 19]. In a retrospective study, Chambers et al. discovered that GERD was the only historic factor that met statistical significance as a predictor of poor symptom outcome after ESS [20]. DelGaudio demonstrated using a specially designed pH probe that patients with medically and surgically refractory CRS had increased reflux at the nasopharynx, upper esophageal sphincter, and distal esophagus when compared to those without sinus disease and those with successful sinus surgery [5].

Although acid suppression therapy for the treatment of CRS seems intuitive, the use of anti-reflux medications in the management of the condition is controversial, in part due to the conflicting epidemiologic evidence linking the two disease processes together [8]. The American Academy of Otolaryngology expert panel in 2014 stated that the lack of randomized, controlled studies supporting a strong relationship between GERD and CRS in the pediatric population does not warrant empiric reflux treatment as adjunctive medical therapy [21]. The Allergy Joint Task Force concurred, stating that there is no evidence that GERD is a significant causal factor of CRS and therefore did not recommend anti-reflux therapy for refractory adult cases [22]. In the setting of ongoing controversy, national practice patterns have not favored reflux treatment for CRS [8]. Several studies have shown that the resolution of extraesophageal manifestations of reflux with proton pump inhibitors

(PPI) has been difficult to achieve. In a small prospective study, DiBaise et al. compared 11 CRS patients with 19 GERD control patients to ascertain whether aggressive anti-reflux therapy could achieve sinus symptom improvement. CRS patients alone received omeprazole 20 mg twice daily for 3 months. Modest symptom improvement was reported, but resolution occurred infrequently in the study group [23]. DelGaudio published similar findings in which only 2 of 38 patients with CRS had dramatic improvement after adequate PPI treatment was initiated [5]. In a multifactorial disease, acid suppression alone may provide partial or no relief of CRS symptoms, as reflux likely represents only one of many contributing factors. In contrast, Pincus et al. found that 14 of 15 patients who were placed on a PPI regimen demonstrated some improvement in their sinus symptoms, including 7 who reported either complete or near-complete resolution of symptoms. Due to these findings, the study concluded that anti-reflux therapy may be beneficial in the treatment of refractory CRS [24].

Conclusion

Many studies have sought to investigate the role of acid reflux in the pathogenesis of CRS, delineate the mechanisms that contribute to the disease process, and examine the efficacy of anti-reflux therapy in disease management. Due to the high prevalence of either entity, a direct relationship between CRS and GERD has been difficult to establish due to the possibility of them coexisting independently. In general, the literature suggests that there is a relationship between reflux and CRS, particularly the subtype that is refractory to medical and surgical treatments. However, the available studies often have small sample sizes, each employing different methodologies that hinder accurate interpretation of the collective data. Therefore, the evidence confirming a definitive causal association is lacking. Furthermore, the data for the effect of PPI therapy on symptom improvement in patients with CRS is conflicting, with multiple professional organizations not recommending the use of anti-reflux medications in the management of the disease. Alternatively, as part of the initial medical management for the treatment of LPR, a dietary approach consisting of alkaline water and a plant-based, Mediterranean-style diet should be attempted. Although the benefit of LPR treatment in modifying the disease course of CRS remains debatable, this diet-based approach confers a host of other health benefits, including a decreased risk of cardiovascular disease, diabetes, stroke, and cancer [25] with potential positive changes to the microbiome creating a more favorable, healthier local microenvironment. To rectify the limitations of the available literature, multicenter studies with a larger number of patients and standardized criteria for diagnosis and methodology would be beneficial.

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