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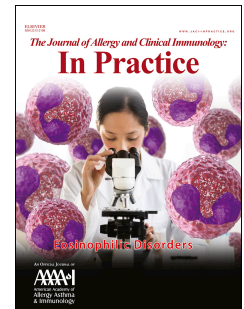
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Persistence of sinonasal disease despite mepolizumab

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Abbreviations: CRS (chronic rhinosinusitis), CRSwNP (chronic rhinosinusitis with nasal polyposis), CRSsNP (chronic rhinosinusitis without nasal polyposis), IL (interleukin), AERD (aspirin exacerbated respiration disease), US (United States), CT (computed tomography), IgE (immunoglobulin E), gastroesophageal reflux disease (GERD), C-ANCA (cytoplasmic anti-neutrophilic cytoplasmic antibody), P-ANCA (perinuclear anti-neutrophilic cytoplasmic antibody), ESS (endoscopic sinus surgery); EoE (eosinophilic esophagitis); kU/L (kilo unit per liter), NSAID-exacerbated respiratory disease (N-ERD); Food and Drug Administration (FDA)

Abstract

The treatment paradigm for the management of chronic rhinosinusitis with nasal polyposis (CRSwNP) is currently undergoing a rapid evolution with the development of monoclonal antibody therapies targeted at type 2 inflammatory pathways. The use of these biologic therapies in asthmatic patients, and more recently, patients with CRSwNP has produced promising results, especially for patients with severe disease. Many questions regarding the appropriate timing of these medications, whether or not these new treatment strategies should be used as a monotherapy or in conjunction with traditional therapies such as sinus surgery, the role of appropriate phenotyping, and identification of biomarkers, remain unanswered. We herein present a case of a patient with severe eosinophilic asthma and comorbid CRSwNP who failed to achieve control of his respiratory symptomology and ultimately progressed to sinus surgery despite treatment with an anti-interleukin 5 monoclonal antibody therapy (mepolizumab). Consideration is given to the mechanistic underpinnings of the reported patient's failure. This case highlights the need for further understanding of the optimal usage of these novel therapeutics in the management of CRSwNP and in the need to better understand the pathophysiology of CRSwNP.

Manuscript

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting more than 10% of the population in western countries^{1,2}, 8-11% of the population in Asia^{3,4}, and roughly 38 million Americans.² Though CRS is diagnosed by a combination of subjective sinonasal symptoms and objective evidence of mucosal inflammation^{5,6}, the implications of this disease extend well beyond the nose and paranasal sinuses. A diagnosis of CRS has wide-reaching impact on patient-reported quality of life, with well-described associations with depression⁷, cognitive impairment^{8,9}, and overall health states equal or worse to other chronic diseases such as congestive heart failure, end-stage renal disease, and chronic obstructive pulmonary disease.^{10,11} CRS also imparts significant socioeconomic implications with an estimated annual overall direct cost of \$10-\$13 billion and indirect costs in excess of \$20 billion per year in the United States (US) alone.¹²

CRS is typically described as one of two characteristic phenotypes, CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). There is marked heterogeneity within the phenotype including variants such as aspirin exacerbated respiration disease (AERD)¹³, also known as NSAID-exacerbated respiratory disease (N-ERD)¹⁴, and allergic fungal rhinosinusitis (AFRS). Epidemiologically, CRSwNP has an estimated prevalence of more than 4% in both the US and Europe¹⁵⁻¹⁷, and is clinically characterized by high recurrence rates despite appropriate medical therapy and endoscopic sinus surgery.¹⁷ Glucocorticoids, topical and oral, are the mainstay of therapy for patients with CRSwNP. Despite medical therapy with glucocorticoids, a significant proportion of patients require sinus surgery in an attempt to improve disease and symptom control.¹⁷

87

88 Beyond the clinical presentation, CRSwNP can also be subdivided into different endotypes based
89 on inflammatory markers. Molecularly, the majority of disease in the western world is marked by
90 a characteristic type 2 inflammatory signature of interleukins (IL) and inflammatory markers,
91 typically IL-4, IL-5, IL-13, and eosinophilia.¹⁸ Nasal polyp tissue from within the paranasal
92 sinuses demonstrates high levels of tissue eosinophils, basophils, and mast cells.¹⁹ In an effort to
93 directly target the underlying mechanism of CRSwNP, there has been an emerging interest in the
94 role of monoclonal antibodies (biologic therapy) aimed at type 2 inflammatory markers. These
95 biologic therapies offer promising results and present a novel, potential treatment option for
96 patients with particularly challenging airway disease.²⁰⁻²² The recent approval by the US Food
97 and Drug Administration (FDA) of dupilumab, with an indication for nasal polyposis, has
98 garnered particular interest.²² Despite encouraging results across the investigations examining
99 these new therapies, relatively little is known about the optimal indications, patient selection, and
100 potentially even untoward effects of these medications. We present a case of a patient with
101 recalcitrant nasal polyposis and severe asthma despite treatment with a mepolizumab.

102

103 *Case presentation*

104

105 A 63-year-old man of European-ancestry with longstanding, severe asthma, persistently elevated
106 immunoglobulin E (IgE) levels, and peripheral eosinophilia presented to his pulmonologist with
107 3-4 annual asthma exacerbations requiring treatment with oral steroids. Despite compliance with
108 multimodal medical therapy including a combination inhaler of budesonide and formoterol, a
109 tiotropium inhaler, and oral montelukast, he remained symptomatic and reported that each of

these episodes was preceded by sinonasal complaints. The patient's history was notable for developing a rash in response to ibuprofen, but he tolerated 162mg aspirin therapy daily for cardiovascular prophylaxis and 220mg naproxen sodium for pain as needed without any respiratory or allergic sequelae. His medical history included hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), benign prostatic hypertrophy, anxiety, and chronic back pain. He had previously undergone several orthopedic surgeries, as well as a remote nasal septoplasty and tonsillectomy. In the setting of poorly controlled respiratory symptoms his pulmonologist considered a differential diagnosis including allergic or occupational-related asthma, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, bronchiectasis, poorly controlled GERD, hypersensitivity pneumonitis, and eosinophilic pneumonia.

Further evaluation included laboratory testing, pulmonary function testing and computed tomography (CT) of the chest. Baseline total IgE level was elevated at 2,361 IU/mL (reference range: 0 - 100 IU/mL) and absolute eosinophil count was elevated at $1.1 \times 10^3/\mu\text{L}$ (normal range: $0.0 - 0.4 \times 10^3/\mu\text{L}$). Cytoplasmic anti-neutrophilic cytoplasmic antibody (C-ANCA), perinuclear anti-neutrophilic cytoplasmic antibody (P-ANCA) and atypical P-ANCA were negative. Prior allergy skin prick testing had been completely negative and a radioallergosorbent test was negative across all allergens with the exception of 2 equivocal IgE levels to *Mucor racemosus* (0.10 kU/L) and *Alternaria alternata* (0.13 kU/L). Pulmonary function testing demonstrated an FEV₁ of 1.64L, a moderate obstructive ventilatory defect without immediate response to inhaled bronchodilators, and a flow-volume loop showed obstruction. A non-contrasted CT chest was negative for interstitial disease, bronchiectasis, pulmonary effusion, lymphadenopathy, or

infiltrates. Nasal endoscopy or CT of the paranasal sinuses was not completed at this point in his workup.

The patient was prescribed a 2-month empiric trial of daily 20mg omeprazole and 10mg loratadine, both of which failed to improve his symptomatology. The decision was then made to pursue 100mg mepolizumab subcutaneous injections to improve asthma control at an interval of every 4 weeks. Mepolizumab is a humanized anti-IL-5 monoclonal antibody with approval for severe eosinophilic asthma. At the time of initiation of mepolizumab, no biologic agent with the specific indication for the treatment of nasal polyposis, had been approved by the FDA. Following initiation of mepolizumab, the patient experienced subjective improvement in asthma-related symptomatology, as well as a corresponding decrease in total IgE level to 494 IU/mL and absolute eosinophil count to $0.1 \times 10^3/\mu\text{L}$, both to within normal range. Nonetheless, despite regular mepolizumab injections for 15 months, the patient continued with periodic acute asthma exacerbations, all of which were heralded by preceding sinonasal symptoms. Each distinct episode was treated with oral antibiotics and oral steroids, most commonly 40mg of prednisone daily for 7 days and amoxicillin-clavulanate 875-125mg twice daily for 10 days. The patient responded favorably to each of these courses of medical therapy, but because of repeated exacerbations with concurrent mepolizumab, the patient was referred to otolaryngology for further evaluation.

Upon presentation to otolaryngology, the patient endorsed longstanding nasal airway obstruction, decreased sense of smell, thick gray anterior and posterior nasal drainage, and facial pressure. At that point, he had continued regular, daily usage of topical fluticasone propionate nasal spray and

156 accompanying nasal saline irrigations. Nasal endoscopy demonstrated abundant secretions,
157 bilateral nasal polyposis, polypoid degeneration of the left middle turbinate, and diffuse bilateral
158 soft tissue swelling that responded poorly to topical decongestants. Nasal polyp score was 2 on
159 each side, for a total score of 4, of a maximum 8. The patient, then 5 weeks status post treatment
160 with oral steroids and antibiotics, underwent a CT of his sinuses (**Figure 1**) that showed bilateral
161 opacification involving all paranasal sinuses and bilateral ostiomeatal complexes with
162 accompanying air-fluid levels within the bilateral maxillary and left sphenoid sinuses, with a
163 Lund-Mackay score²³ of 19/24.

164
165 Treatment options presented to the patient included continued therapies including oral steroids,
166 antibiotics for bacterial flare-ups, or endoscopic sinus surgery (ESS). Other options included
167 macrolide therapies for their anti-inflammatory response, large volume saline irrigations
168 combined with budesonide or mometasone; or alternate steroid delivery systems such as an
169 exhaled delivery system. Finally, a trial of another monoclonal antibody with a different
170 mechanism of action and target, was considered.

171
172 After reviewing the potential treatment options and discussing the risks and benefits of surgery,
173 the patient elected to undergo bilateral ESS. Surgery was uneventful and showed bilateral nasal
174 polyposis obstructing the sinus ostia, with thick mucus in multiple sinuses. Intraoperative
175 cultures from multiple sinuses were negative other than very light growth of *Staphylococcus*
176 *lugdunensis* and coagulase negative *Staphylococcus* species. All fungal cultures were negative.
177 Pathology (**Figure 2**) was notable for a single focus of eosinophils, but otherwise scant
178 inflammatory infiltrate comprised of lymphocytes and plasma cells without appreciable mast

cells or basophils, though specialized staining was not undertaken. Overall, the histology was generally mild and bordered on normal, despite the patient's clinical presentation.

The role of monoclonal antibodies for the treatment of CRSwNP and asthma

This case illustrated how sinus disease can exacerbate asthma. There is a mounting body of evidence demonstrating that improved control of sinonasal disease in patients with CRSwNP improves asthma disease severity and quality of life.^{24,25} Reciprocally, acute exacerbations of CRS are negatively associated with control of asthma.²⁶ Taken together, this underscores the importance of sinonasal disease control and management in the asthmatic patient.

The overlapping features and continuum of airway disease between CRSwNP and asthma have long been recognized.²⁷⁻²⁹ Immunologically, both CRSwNP and asthma are thought to be primarily T_H2-mediated processes with inflammatory signatures characterized by IL-4, IL-5, IL-13 and eosinophilia, though there are components of T_H1 and T_H17 in these pro-inflammatory airway diseases.¹⁸ On a molecular level, biopsies of nasal polyps and bronchial tissue demonstrate similar T_H2 cytokine profiles.³⁰ Prior work has also demonstrated distinct clustering of CRS patients based on the characterization of nasal polyp inflammatory milieu and the presence or absence of asthma, suggesting that endotyping, rather than phenotypic descriptions alone, may provide better insight into a patient's disease.³¹

In addition to traditional treatment strategies, biologic, monoclonal antibodies were first approved for the treatment of recalcitrant asthma nearly 20 years ago. Since their inception, there

has been an increasing number of available biological therapies targeting T_H2-mediators, such as anti-IgE³², anti-IL4R α ³³, anti-IL5³⁴, and anti-IL5R α .³⁵ In the asthmatic patient population, these biologics decrease respiratory exacerbations, oral steroid usage and rescue medications, while improving quality of life.³⁶ Several biologics have current approval for asthma, atopic dermatitis, and urticaria, however, dupilumab became the first monoclonal antibody to gain FDA-approval with a primary indication for the treatment of nasal polyposis.²² Nonetheless, secondary outcomes in asthma-focused trials, and a number of ongoing or recently completed clinical trials investigating the use of biologics for the management of CRSwNP, have demonstrated promising results for this patient population.^{20,32,37,38}

To review, the patient in this current report presented with severe, persistent eosinophilic asthma and CRSwNP who failed appropriate and maximal medical therapy. He was started on an anti-IL-5 biologic therapy (mepolizumab) in the setting of poor asthma control, high IgE levels and peripheral eosinophilia. Though the patient had initial subjective improvement, as well as a dramatic normalization in total IgE levels and absolute eosinophil counts, the patient continued with persistent sinonasal exacerbations, and associated continued poor control of asthma when his rhinosinusitis flared. The patient improved both in the upper and lower airway with medical management for the treatment of his upper respiratory exacerbations, but ultimately progressed to sinus surgery in the setting of poor overall sinonasal disease control. Finally, rather than the characteristic eosinophil-laden nasal polyposis that we anticipated in this patient, pathology was notable for a generalized lack inflammatory infiltrate. On hematoxylin and eosin stain, there was a single focus of eosinophils in the examined tissue and no evidence of mast cells or basophils. The overall histopathology bordered on normal. This suggests that medical management had

controlled at least part of the inflammation within the polyps. This concept is further supported by the dramatic improvement in this patient's total IgE and absolute eosinophil counts.

In the setting of persistent, obstructive nasal polyposis, the patient's paranasal sinus ostia remained blocked, and he continued with the characteristic persistent symptomatology of patients with recalcitrant CRSwNP punctuated by episodes of acute exacerbations. Two randomized, double-blind, placebo-controlled trials examining the use of mepolizumab in the treatment of CRSwNP showed improvement in nasal endoscopy scores, radiologic scores, and sinonasal-related quality of life measures.^{37,38} Not all patients in these studies responded uniformly to mepolizumab. In one study, patients receiving mepolizumab had a 60% improvement in nasal polyp and radiologic scores as compared to 10% of controls that demonstrated a similar improvement.³⁸ Meanwhile, a second study demonstrated that after 25 weeks, 30% of the patients receiving mepolizumab were no longer considered surgical candidates, compared to only 10% of controls.³⁷ In the referenced studies, it is unknown if histopathological analysis would have been similar to our current case that was devoid of inflammatory infiltrate within the patient's nasal polyps. It is however worth noting that the standard 100 mg asthma dosage of mepolizumab, which this patient received, is lower than the 750mg dosages of mepolizumab used in the reported trials for patients with CRSwNP.^{37,38} While dose may explain the discrepancy in our patient, the postoperative pathology suggested the dose was adequate to remove the eosinophils and the inflammatory infiltrate from the nasal polyp tissue. It is also possible that oral steroids reduced the eosinophils in the nasal polyp tissue. An investigation with dexamipexole, similarly to our case, depleted eosinophils but did not impact nasal polyp size, suggesting that eosinophilic inflammation does not contribute to nasal

polyp mass in all patients with CRSwNP.³⁹ Another important consideration is that other inflammatory cells, such as mast cells and basophils, not targeted by mepolizumab, contributed to the patient's recalcitrant disease.⁴⁰⁻⁴²

This patient's course raises the question of creation of a new clinical scenario. After treatment with mepolizumab, this patient's nasal polyp histology was devoid of the characteristic type 2 inflammation and the histology more closely resembled normal tissue. While it is possible that the reduced inflammatory markers within the nasal polyps on histology was potentially secondary to repeated courses of oral steroids, this would be unusual for a patient with recalcitrant nasal polyposis. Moreover, though not confirmed with a tissue diagnosis of fibrin deposition, clinically, the nasal polyps were somewhat firm and fibrotic. Prior investigations have recognized excess deposition of fibrin in nasal polyp tissue as a pathologic hallmark of the disease.⁴³ Moreover, findings in both CRS and asthma literature demonstrate local dysregulation of the coagulation cascade and impaired fibrinolysis.⁴⁴⁻⁴⁶ Nonetheless, the clinical implications of this dysfunction and the potential interaction these altered processes may have with biologic therapies remains unknown. Though one can speculate that they contribute to the mass of the nasal polyp tissue.

Emerging evidence suggests that eosinophilia may induce fibrosis. Data from the eosinophilic esophagitis (EoE) literature demonstrates that EoE has a spectrum of disease severity, presenting as one of 3 distinct endotypes. Overall, EoE shares many similarities to CRSwNP in that they are both T_H2-mediated chronic inflammatory conditions marked by eosinophilia and eosinophilic-inflammation.⁴⁷ Though EoE may begin as a benign, inflammatory condition, it may ultimately

progress to a distinct fibrostenotic disease.⁴⁸ This transformation can be mimicked in animal models, which demonstrate that chronic overexpression of eosinophils, mast cells, IL-5, and IL-13 is associated with extensive esophageal remodeling and histologic changes of fibrostenosis.⁴⁷ A recent report identifies an upregulated esophageal epithelial gene that appears to be associated with increased levels of cross-linked collagen, thereby inciting fibrosis of the esophageal lamina propria.⁴⁸ Though the findings in the EoE literature are intriguing, a similar mechanism has not yet been identified in CRSwNP. Nonetheless, if there were a shared mechanism between these 2 distinct clinical phenotypes, and the sinonasal mucosa in patients with CRSwNP responded akin to esophageal mucosa in patients with EoE, a similar end-stage manifestation of fibrosis could occur in both patient populations. In our presented case, this concept may help to explain why despite appropriate usage of mepolizumab, coupled with objective improvement in eosinophilic inflammation, the patient continued with recalcitrant symptomology.

The observation of this patient's clinical conundrum introduces some timely questions regarding the pathogenesis and management of CRSwNP, on the eve of a potential revolution of CRSwNP treatment paradigms in the era of biologic therapies. For instance, could the long duration of eosinophilic inflammation in our patient prior to mepolizumab treatment have induced fibrosis in the nasal polyps preventing their complete resolution despite the successful reduction in eosinophilic inflammation? Would the patient have responded to another biologic therapy with a different mechanism of action? Moreover, would the introduction of mepolizumab earlier in this patient's disease have prevented fibrosis of his nasal polyposis and thereby improved his sinonasal response to mepolizumab? The optimal timing of these medications is unknown, and it will be interesting to observe whether the use of other biologics will lead to similar scenarios.

Finally, it remains to be seen whether the use of mepolizumab postoperatively will prevent the recurrence of nasal polyps.

There are currently multiple clinical trials examining the use of biologics for patients with nasal polyposis and there will be future trials with newer biologic agents. The patient in this report highlights the importance of long-term follow-up and assessment. Knowing the duration of nasal polyposis before initiation of therapy with a biologic also appears to potentially be an important factor in disease management. One wonders about the role and timing of surgical intervention in the overall management of nasal polyps. Should surgery be done before initiation of biologics in cases of massive nasal polyposis? Though prior studies suggested improved postoperative outcomes in patients who undergo earlier surgical intervention^{49,50}, more recent evidence is conflicting.⁵¹ The inclusion criteria of some clinical trials of biologics limit enrollment to patients with prior sinus surgery. Is this based on the observation that fibrosis within longstanding nasal polyps prevents obtaining optimal patient outcomes? Is this why aspirin desensitization in patients with AERD is used primarily postoperatively? Is this the underlying principle driving the suggestion to widely open the frontal sinus in patients with CRSwNP to lessen recurrence rates? Should patients with non-eosinophilic nasal polyps do better with surgical intervention? These questions, along with a long list of unmet needs, such as identification of biomarkers and an improved understanding of treatment outcomes that relate to asthma, quality of life and olfaction, will be vital in our understanding of the role of biologics in the management of CRS. The increasing familiarity with biologics and targeted scientific inquiry will help to answer these essential questions.

Summary

In this report, a patient with severe eosinophilic asthma and CRSwNP was started on mepolizumab to control his recalcitrant airway disease. Despite improvements in laboratory values suggesting that this targeted therapy did improve eosinophilic-related inflammation, the patient continued to have obstructive nasal polyposis and this treatment modality did not improve this patient's CRSwNP or pulmonary exacerbations. The patient ultimately required surgical intervention in the form of ESS, showing tissue histology devoid of eosinophilia, suggesting the medication had achieved its intended effect, without meaningful improvement in nasal polyposis. We suspect that tissue fibrosis or a similar mechanism may have contributed to the mass of the nasal polyps causing mechanical obstruction of the sinus ostia causing impairment of mucus drainage. A current and ongoing debate surrounds the question of the appropriate timing with the use of these new biologics and whether these therapies should be used in conjunction with ESS or as a standalone therapy. This case underscores the need for further defining appropriate clinical care pathways involving multiple disciplines and the identification of biomarkers for the use of these medication.

References:

1. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. *Allergy*. 2011;66(9):1216-23.
2. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. *Vital and health statistics Series 10, Data from the National Health Survey*. 2014(260):1-161.
3. Kim JH, Cho C, Lee EJ, Suh YS, Choi BI, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in South Korea according to diagnostic criteria. *Rhinology*. 2016;54(4):329-35.
4. Shi JB, Fu QL, Zhang H, Cheng L, Wang YJ, Zhu DD, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy*. 2015;70(5):533-9.
5. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2015;152(2 Suppl):S1-s39.
6. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1-12.
7. Schlosser RJ, Hyer JM, Smith TL, Mace JC, Cortese BM, Uhde TW, et al. Depression-Specific Outcomes After Treatment of Chronic Rhinosinusitis. *JAMA otolaryngology-- head & neck surgery*. 2016;142(4):370-6.

8. Yoo F, Schlosser RJ, Storck KA, Ganjaei KG, Rowan NR, Soler ZM. Effects of endoscopic sinus surgery on objective and subjective measures of cognitive dysfunction in chronic rhinosinusitis. *International forum of allergy & rhinology*. 2019;9(10):1135-43.
9. Rowan NR, Schlosser RJ, Storck KA, Ganjaei KG, Soler ZM. The impact of medical therapy on cognitive dysfunction in chronic rhinosinusitis. *International forum of allergy & rhinology*. 2019;9(7):738-45.
10. Soler ZM, Wittenberg E, Schlosser RJ, Mace JC, Smith TL. Health state utility values in patients undergoing endoscopic sinus surgery. *The Laryngoscope*. 2011;121(12):2672-8.
11. Remenschneider AK, D'Amico L, Gray ST, Holbrook EH, Gliklich RE, Metson R. The EQ-5D: a new tool for studying clinical outcomes in chronic rhinosinusitis. *The Laryngoscope*. 2015;125(1):7-15.
12. Rudmik L. Economics of Chronic Rhinosinusitis. *Current allergy and asthma reports*. 2017;17(4):20.
13. Laidlaw TM, Boyce JA. Aspirin-Exacerbated Respiratory Disease--New Prime Suspects. *The New England journal of medicine*. 2016;374(5):484-8.
14. Kowalski ML, Agache I, Bavbek S, Bakirtas A, Blanca M, Bochenek G, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. *Allergy*. 2019;74(1):28-39.
15. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *The Journal of allergy and clinical immunology*. 1977;59(1):17-21.
16. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *International journal of epidemiology*. 1999;28(4):717-22.

17. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *The Laryngoscope*. 2017;127(3):550-5.
18. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *International forum of allergy & rhinology*. 2016;6 Suppl 1:S22-209.
19. Schleimer RP. Immunopathogenesis of Chronic Rhinosinusitis and Nasal Polyposis. *Annual review of pathology*. 2017;12:331-57.
20. Tsetsos N, Goudakos JK, Daskalakis D, Konstantinidis I, Markou K. Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review. *Rhinology*. 2018;56(1):11-21.
21. Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019.
22. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet (London, England)*. 2019.
23. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology*. 1993;31(4):183-4.
24. Schlosser RJ, Smith TL, Mace J, Soler ZM. Asthma quality of life and control after sinus surgery in patients with chronic rhinosinusitis. *Allergy*. 2017;72(3):483-91.
25. Phillips KM, Hoehle LP, Bergmark RW, Campbell AP, Caradonna DS, Gray ST, et al. Chronic rhinosinusitis severity is associated with need for asthma-related systemic corticosteroids. *Rhinology*. 2017;55(3):211-7.

26. Banoub RG, Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Relationship between chronic rhinosinusitis exacerbation frequency and asthma control. *The Laryngoscope*. 2018;128(5):1033-8.
27. Massoth L, Anderson C, McKinney KA. Asthma and Chronic Rhinosinusitis: Diagnosis and Medical Management. *Medical sciences (Basel, Switzerland)*. 2019;7(4).
28. Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *American journal of rhinology & allergy*. 2011;25(4):205-8.
29. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical Characteristics of Patients with Chronic Rhinosinusitis with Nasal Polyps, Asthma, and Aspirin-Exacerbated Respiratory Disease. *The journal of allergy and clinical immunology In practice*. 2017;5(4):1061-70.e3.
30. Hakansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, et al. Airway Inflammation in Chronic Rhinosinusitis with Nasal Polyps and Asthma: The United Airways Concept Further Supported. *PloS one*. 2015;10(7):e0127228.
31. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *The Journal of allergy and clinical immunology*. 2016;137(5):1449-56.e4.
32. Bidder T, Sahota J, Rennie C, Lund VJ, Robinson DS, Kariyawasam HH. Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together-a real life study. *Rhinology*. 2018;56(1):42-5.

33. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *The New England journal of medicine*. 2018;378(26):2486-96.
34. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *The Journal of allergy and clinical immunology*. 2019;143(5):1742-51.e7.
35. Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. *The Journal of allergy and clinical immunology*. 2018;141(4):1529-32.e8.
36. Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative Efficacy of Anti IL-4, IL-5 and IL-13 Drugs for Treatment of Eosinophilic Asthma: A Network Meta-analysis. *Lung*. 2018;196(5):517-30.
37. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. *The Journal of allergy and clinical immunology*. 2017;140(4):1024-31.e14.
38. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *The Journal of allergy and clinical immunology*. 2011;128(5):989-95.e1-8.
39. Laidlaw TM, Prussin C, Panettieri RA, Lee S, Ferguson BJ, Adappa ND, et al. Dexpiromipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. *The Laryngoscope*. 2019;129(2):E61-e6.

40. Shaw JL, Ashoori F, Fakhri S, Citardi MJ, Luong A. Increased percentage of mast cells within sinonasal mucosa of chronic rhinosinusitis with nasal polyp patients independent of atopy. *International forum of allergy & rhinology*. 2012;2(3):233-40.
41. Takabayashi T, Kato A, Peters AT, Suh LA, Carter R, Norton J, et al. Glandular mast cells with distinct phenotype are highly elevated in chronic rhinosinusitis with nasal polyps. *The Journal of allergy and clinical immunology*. 2012;130(2):410-20.e5.
42. Mahdavinia M, Carter RG, Ocampo CJ, Stevens W, Kato A, Tan BK, et al. Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. *The Journal of allergy and clinical immunology*. 2014;133(6):1759-63.
43. Takabayashi T, Kato A, Peters AT, Hulse KE, Suh LA, Carter R, et al. Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression. *American journal of respiratory and critical care medicine*. 2013;187(1):49-57.
44. Imoto Y, Kato A, Takabayashi T, Stevens W, Norton JE, Suh LA, et al. Increased thrombin activatable fibrinolysis inhibitor (TAFI) in chronic rhinosinusitis with nasal polyps. *The Journal of allergy and clinical immunology*. 2019.
45. Gabazza EC, Taguchi O, Tamaki S, Takeya H, Kobayashi H, Yasui H, et al. Thrombin in the airways of asthmatic patients. *Lung*. 1999;177(4):253-62.
46. Schouten M, MA VDP, Levi M, T VDP, JS VDZ. Early activation of coagulation after allergen challenge in patients with allergic asthma. *Journal of thrombosis and haemostasis : JTH*. 2009;7(9):1592-4.
47. O'Shea KM, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology*. 2018;154(2):333-45.

- 468 48. Ben Baruch-Morgenstern N, Shoda T, Rothenberg ME. Bagels and LOX in patients with
469 eosinophilic esophagitis. *The Journal of allergy and clinical immunology*. 2019;144(1):41-3.
- 470 49. Hopkins C, Andrews P, Holy CE. Does time to endoscopic sinus surgery impact
471 outcomes in chronic rhinosinusitis? Retrospective analysis using the UK clinical practice
472 research data. *Rhinology*. 2015;53(1):18-24.
- 473 50. Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes
474 in Chronic Rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery
475 for Nasal Polyposis and Chronic Rhinosinusitis. *Rhinology*. 2015;53(1):10-7.
- 476 51. Alt JA, Orlandi RR, Mace JC, Soler ZM, Smith TL. Does Delaying Endoscopic Sinus
477 Surgery Adversely Impact Quality-of-Life Outcomes? *The Laryngoscope*. 2019;129(2):303-11.

Figure Legends

Figure 1. Non-contrasted CT scan of the sinuses with a) axial section demonstrating air-fluid levels in the maxillary sinuses and b) coronal reformat with complete opacification of the ethmoid sinuses and c) sagittal reformats demonstrating complete opacification of the ethmoid and frontal sinuses, with circumferential mucosal thickening in the left sphenoid sinus. Lund-Mackay score: 19/24.

Figure 2. Hematoxylin and eosin stain of sinonasal mucosa and nasal polyps removed following endoscopic sinus surgery and failed biologic therapy. Histopathology revealed minimal inflammatory infiltrate, bordering of normal tissue architecture, with a single focus of eosinophils, but no evidence of mast cells or basophils.

