

Aspirin-Exacerbated Respiratory Disease With Allergic Fungal Rhinosinusitis: A Case Series of Overlapping Sinonasal Endotypes

Matthew B. Studer, BA¹, Lauren T. Roland, MD, MSCI² ,
Matthew C. Ochsner, MD³, Daniel Cox, MD⁴,
John M. DelGaudio, MD³, Sarah K. Wise, MD, MSCR³, and
Joshua M. Levy, MD, MPH³ 

Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous inflammatory disease with multiple underlying etiologies. Although several CRSwNP endotypes have been detailed, the current classification system does not adequately represent all patients with nasal polyps. We describe 2 patients meeting established diagnostic criteria for both aspirin-exacerbated respiratory disease (AERD) and allergic fungal rhinosinusitis (AFRS), which are considered distinct CRSwNP endotypes.

Objective: To describe patients meeting established diagnostic criteria for both AERD and AFRS in order to highlight deficits in the current CRSwNP endotype classification system as well as to expand awareness of the potential for aspirin desensitization as a treatment option in a subset of patients with AFRS.

Methods: Retrospective chart review with description of patient and diagnostic characteristics. AERD was diagnosed based on the presence of nasal polyps, asthma, and a documented history of sensitivity to nonsteroidal anti-inflammatory drugs. AFRS was diagnosed based on Bent and Kuhn criteria.

Results: Patients met established diagnostic criteria for both AERD and AFRS. Microscopic examination of sinus tissue revealed reactive bone, tissue eosinophilia (>10/high-powered field), and allergic mucin with noninvasive fungal elements. Subjects had an average of 4 endoscopic sinus surgeries and are currently maintained with adjunctive aspirin desensitization and/or anti-IL-5 biologic therapy.

Conclusions: This case series suggests that although they are treated as distinct CRSwNP endotypes, AERD and AFRS may have more overlap than was previously appreciated. Further research is needed to accurately identify discrete endotypes and associated treatment outcomes as we seek individualized patient care.

Keywords

chronic rhinosinusitis, aspirin-exacerbated respiratory disease, allergic fungal rhinosinusitis, diagnosis, endotype, nasal polyps, asthma, NSAIDs, aspirin challenge, desensitization

Introduction

Chronic rhinosinusitis (CRS) is a common condition thought to affect approximately 5% of the US population and represents a significant burden to the healthcare system.^{1–3} Historically, treatment recommendations have been limited to CRS phenotype, denoted by the presence or absence of nasal polyps, a practice which constrains the diverse group of patients with CRS with nasal polyps (CRSwNP) into a single characterization.⁴ Rather than representing a single disease, CRSwNP is associated with several different etiologies and

¹Emory University School of Medicine, Atlanta, Georgia

²Department of Otolaryngology-Head and Neck Surgery, University of California San Francisco, San Francisco, California

³Department of Otolaryngology-Head and Neck Surgery, Emory University, Atlanta, Georgia

⁴Intermountain Healthcare, Murray, Utah

Corresponding Author:

Lauren T. Roland, University of California San Francisco, 2233 Post Street, San Francisco, CA 94115, USA.

Emails: lauren.tashima.roland@gmail.com; lauren.roland@ucsf.edu

pathological states, including cystic fibrosis, allergic fungal rhinosinusitis (AFRS), aspirin-exacerbated respiratory disease (AERD) and others.⁵ Following an increased awareness of the diversity of conditions associated with CRSwNP and an expanding emphasis on personalized medicine, there is a movement to characterize patients based on their underlying endotype or pathophysiologic mechanism of disease.

AERD and AFRS are 2 of the most recalcitrant CRSwNP endotypes. Their pathophysiology has been previously studied, leading to the current understanding of each as a mechanistically distinct disease. AERD is characterized by progressive inflammation of both upper and lower airways with asthma, CRSwNP, and sensitivity to aspirin and other cyclooxygenase-1 inhibitors.⁶ AERD is not hypothesized to be the result of a traditional, immunoglobulin E (IgE)-mediated hypersensitivity reaction. Rather, abnormalities in arachidonic acid metabolism result in the overproduction of the cysteinyl leukotrienes.⁷ This overproduction is emphasized when the patient consumes cyclooxygenase-inhibiting drugs. Why this reaction occurs in patients with AERD and not in the general population is not fully understood, but it may relate to the overexpression of the cysteinyl leukotriene receptor 1 and leukotriene C4 synthase.⁸ Requirements for a clinical diagnosis of AERD are shown in Table 1. A positive oral aspirin challenge represents the gold standard for diagnosis.⁹

Table 1. Diagnostic Criteria for AERD and AFRS.

AERD	AFRS
	Major criteria
Chronic rhinosinusitis with nasal polyps	Nasal polyposis
	Type I IgE-mediated hypersensitivity to fungi
Moderate to severe asthma	Typical computed tomography signs
	Eosinophilic mucus without fungal invasion
One or more respiratory reaction following NSAID exposure with or without gastrointestinal symptoms	Positive fungal stain
	Minor criteria
	Positive fungal culture
	Asthma
	Unilateral predominance
	Radiographic bone erosion
	Charcot-Leyden crystals
	Serum eosinophilia

Abbreviations: AERD, aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis.

Patients included in this study met at least all 3 AERD criteria and all 5 AFRS major criteria. Findings listed under minor criteria are supportive but not necessary for a diagnosis of AFRS.

AFRS appears to be mediated by a sinonasal hypersensitivity reaction to communal fungal allergens. Initial reports described Gell and Coombs type I and III reactions, but alternative theories suggest a T-cell-mediated type IV reaction or a localized type I reaction.¹⁰ Most AFRS patients exhibit significant positive responses on allergy skin testing, indicating IgE-mediated reactivity. Bent and Kuhn criteria are utilized to confirm AFRS, as shown in Table 1.¹¹

It is imperative to clearly define unique CRSwNP endotypes in order to individualize patient treatment and improve outcomes. In this case series, we describe 2 patients who meet current diagnostic criteria for both AERD and AFRS.

Methods

Exemption from institutional review board oversight was obtained from the Emory University Biomedical Institutional Review Board. A single institution retrospective chart review was completed from January 2018 to March 2019. The review focused on patients identified in clinic by faculty during this timeframe that were deemed to potentially have both AFRS and AERD. Chart review was utilized to confirm that all criteria were met. AFRS was diagnosed based on Bent and Kuhn criteria (Table 1). AERD was diagnosed based on presence of nasal polyps, reported history of NSAID sensitivity, and clinical history of asthma. Asthma was defined by prior diagnosis and concurrent use of inhaled bronchodilators. NSAID sensitivity was defined by either an oral aspirin provocation challenge or reported history of acute respiratory reactions following NSAID ingestion. Atopic status was confirmed by positive allergy testing to fungi or reported positive skin testing. Patients who met criteria for both AERD and AFRS were included. Collected variables for qualitative analysis included demographics, medical/surgical history, clinical findings, and quality-of-life metrics, including 22-item sinonasal outcome test (SNOT-22) scores.¹²

Patients and Results

Two patients met criteria for both AERD and AFRS (Table 2). In brief, both subjects presented for rhinologic care with recurrence of obstructive nasal polyps following previous sinus surgery.

Computed Tomography Findings

Computed tomography (CT) findings were consistent with a presumed diagnosis of AFRS, including multifocal polypoid and high-density opacities throughout the nasal cavity and sinuses with paranasal sinus expansion and associated desossification (Figure 1).

Unfortunately, original CTs were not available for these patients, who were referred to our clinic following previous treatment. CT findings are less well defined in AERD and may affect the expected AFRS findings in these particular patients.

Microscopy Findings

Microscopic examination of sinonasal mucosa revealed reactive bone, tissue eosinophils >10 /high-powered field, eosinophils within overlying surface epithelium, basement membrane thickening, and aggregates of extracellular mucin with positive Grocott's methenamine silver (GMS) fungal stains, all characteristic of AFRS (Figure 2).

Table 2. Clinical Findings of Included Patients.

	Patient 1	Patient 2
Age when AERD criteria fully met	48	16
Age when AFRS criteria fully met	45	18
Age at time of chart review	49	19
Number of sinus surgeries	4	4
Aspirin sensitivity evaluation	Reported history	Aspirin challenge
IgE serum levels	254.0 IU/mL (high)	Not available
Serum absolute eosinophil count	440 cells/ μ L (high)	Not available
Lund-McKay score	22	18
Aspirin desensitization	No	Yes
Method of allergy immunotherapy	sublingual	subcutaneous
Biologic usage	Reslizumab	None
Initial SNOT-22 score	41	83

Abbreviations: AERD, aspirin-exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; IgE, immunoglobulin E; SNOT-22, 22-item sinonasal outcome test.

SNOT-22 scores are representative of symptoms within 3 months of receiving both diagnoses.

Treatment Outcomes

Following revision surgery, patient 1 was treated with sublingual allergy immunotherapy, budesonide irrigations and Reslizumab, and required an in-office procedure for reduction of nasal polyps. Patient 2 was treated with subcutaneous allergy immunotherapy and remains on aspirin 350 mg orally twice a day after desensitization. She has required budesonide irrigations and oral steroid bursts for symptom management. Immunotherapy for both patients included fungal antigens as well as other allergens, such as dust mites, cockroaches, and various weeds.

Discussion

This study represents the first case series of patients meeting diagnostic criteria for both AFRS and AERD. This is a significant finding with both diagnostic and treatment implications for patients with recalcitrant CRSwNP. The potential overlap of these diseases raises questions regarding currently accepted disease endotypes and the innate predisposition to both diseases.

Through a variety of treatments determined by patient preference and the treating rhinologist, both of our patients have shown dramatic improvement of symptoms. Both underwent allergy immunotherapy. Interestingly, one patient underwent aspirin desensitization and maintenance, while the other patient has been treated with biologics, both with excellent results. As biologics are emerging as an exciting option for polyp patients, the cost-effectiveness and safety of both biologics and aspirin desensitization are an area of future investigation.

The overlap of AERD and AFRS has been previously proposed; however, the pathophysiology of this

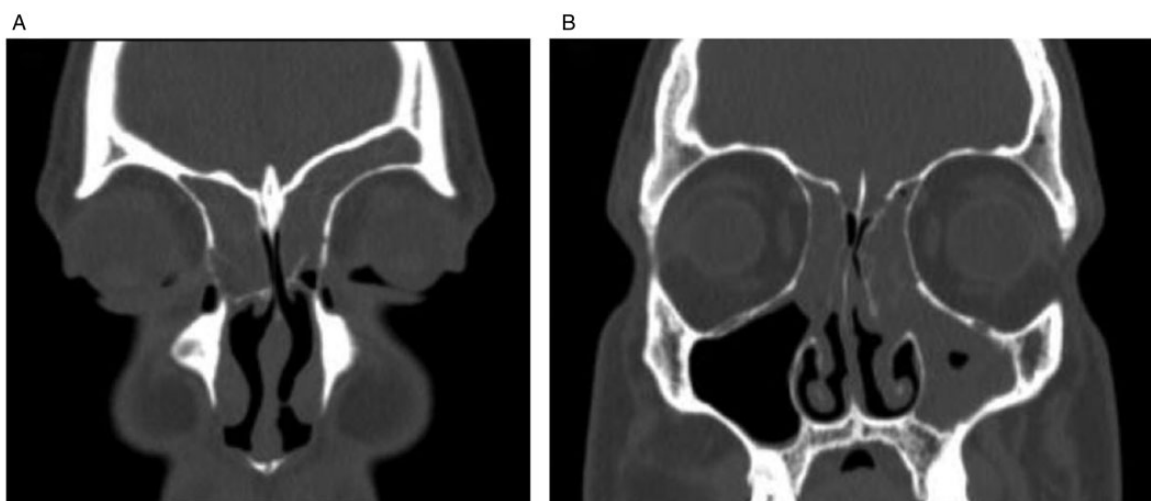


Figure 1. CT findings. A, Patient 1: Expansion of the frontal sinus. B, Patient 2: High-density opacities of the ethmoid sinuses.

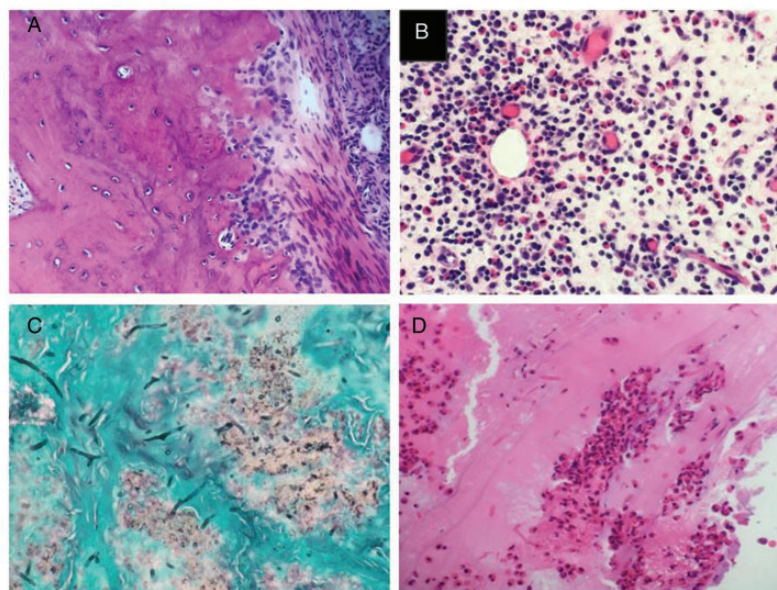


Figure 2. Histopathology findings. A, Patient 1: Reactive bone. B, Tissue eosinophilia (>10 /high-powered field). C, Patient 2: Grocott's methenamine silver (GMS) staining with fungal elements. D, Patient 2: Charcot-Leyden crystals.

comorbid state remains unclear. Both Philpott et al. and Cody et al. showed an increased prevalence of asthma and aspirin sensitivity among patients with AFRS.^{13,14} These studies did not explicitly evaluate an overlap between AERD and AFRS but suggested that AFRS patients had independently higher rates of asthma as well as higher rates of aspirin allergy as compared to other CRSwNP patients. Another case report describes a patient with both aspirin-induced asthma and allergic bronchopulmonary aspergillosis, which is similar to AFRS, but instead targets the lower airway.¹⁵ However, a large recent prospective study involving 410 patients identified significantly decreased rates of confirmed asthma in AFRS patients as compared to other CRSwNP patients.¹⁶ The true prevalence of asthma in AFRS patients is unknown. Chakrabarti et al. described a subset of AERD patients with fungal hyphae identified in mucus but did not further characterize whether or not this subset met the complete criteria for AFRS.¹⁷

It is possible that the clinical manifestations of one disease increase the risk of progression to the second. In vitro studies have shown that fungal reactions lead to production of cysteinyl leukotrienes and prostaglandins.¹⁸ Cysteinyl leukotriene and prostaglandin levels are altered in AERD patients at baseline, predisposing to the characteristic reactions when exposed to NSAIDs.¹⁹ Aspirin sensitivity is thought to be acquired, and this development could potentially be influenced in a subset of patients with AFRS. The hypothesis that AFRS is a risk factor for the development of AERD is supported by the fact that the average age of diagnosis

for AFRS is less than 30 years of age while AERD is usually diagnosed later in life, with an average age of diagnosis of 34 years.^{20,21} How AFRS differs from other endotypes of CRSwNP regarding risk of developing aspirin sensitivity is unclear and deserving of future study. It is also possible that in regions with high fungal concentrations and higher incidences of AFRS, polyps and nasal obstruction lead to an increased risk of inhaled fungal trapping, predisposing AERD patients to AFRS. It has been shown that AFRS has a higher incidence in the southern US states, such as the location of the current study.²² A third possibility is that this case series identified patients with 2 separate disease states, which are genetically unrelated and have completely separate pathophysiology.

AERD and AFRS have previously been defined as separate clinical entities. However, a clinical overlap of these disease states may be overlooked, limiting the potential for disease specific interventions and improved patient outcomes. While the treatment options are similar for AERD and AFRS, aspirin challenge and desensitization may not be considered in AFRS patients who do not report difficulty with NSAIDs. Aspirin sensitivity may present later in life, after AFRS has been diagnosed, and should be readdressed even if prior clinical history or challenge were negative. In addition, biologic therapies targeting the contributing type 2 inflammatory pathways may be considered, although clear indications and patient outcomes are yet to be defined.

There are several limitations of this study. As with all retrospective reviews, we are dependent on the completeness of the medical records. While all patients had

reported aspirin sensitivity and asthma, data were limited regarding confirmatory aspirin challenge and methacholine challenge studies. We believe this is a significant limiting factor as the omission of diagnostic criteria from the medical record, such as documented allergy testing, led to the exclusion of several subjects with suspected overlapping disease. Prospective study is needed to further define prevalence among patients with CRSwNP.

Further work is needed to better understand these 2 CRSwNP diseases and their potential relationship. Proposed research would include the evaluation of leukotriene levels and the prevalence of asthma in patients with AFRS. In addition, a large database study would help identify the incidence of patients with both AERD and AFRS, and the timeline of diagnosis of each disease. A better understanding of the genetics and immunologic pathophysiology of these 2 diseases is also warranted. Increased understanding will lead to better care and treatment of patients with CRSwNP.

Conclusion

In this study, we report a potential association of 2 distinct CRSwNP endotypes. Further research is needed to understand the relationship between these 2 diseases, to both improve accuracy of diagnosis, and targeted treatment options.

Authors' Note

Preliminary data have been presented at the 2018 AAOA conference (poster).

Acknowledgments

The authors extend their special thanks to Dr Kelly Magliocca for her histopathology contributions.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Levy is supported by the Triological Society Research Career Development Award and NIH grants KL2TR002381 and UL1TR002378. Wise is a consultant (Stryker, NeurENT) and a member of Scientific Advisory Board (OptiNose, SinopSys Surgical, ALK-Abello). DelGaudio is a consultant (Medtronic) and receives research support (Spirox). The rest of the authors report no conflicts of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Lauren T. Roland  <https://orcid.org/0000-0003-2036-7611>
Joshua M. Levy  <https://orcid.org/0000-0001-5907-3421>

References

- Orlandi RR, Kingdom TT, Smith TL, et al. International Consensus Statement on Allergy and Rhinology: rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(S1):S22–S209.
- Tan BK, Chandra RK, Pollak J, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2013;131:1350–1360.
- Bhattacharyya N. Assessing the additional disease burden of polyps in chronic rhinosinusitis. *Ann Otol Rhinol Laryngol*. 2009;118:185–189.
- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 Suppl):S1–S39.
- Steinke JW, Borish L. Chronic rhinosinusitis phenotypes. *Ann Allergy Asthma Immunol*. 2016;117:234–240.
- Samter M, Beers RF. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann Intern Med*. 1968;68:975–983.
- Steinke JW, Borish L. Factors driving the aspirin exacerbated respiratory disease phenotype. *Am J Rhinol Allergy*. 2015;29(1):35–40.
- Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med*. 2002;347(19):1493–1499.
- White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med*. 2018;379(11):1060–1070.
- Glass D, Amedee RG. Allergic fungal rhinosinusitis: a review. *Ochsner J*. 2011;11(3):271–275.
- Bent JP III, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg*. 1994;111(5):580–588.
- Rudmik L, Hopkins C, Peters A, Smith TL, Schlosser RJ, Soler ZM. Patient-reported outcome measures for adult chronic rhinosinusitis: a systematic review and quality assessment. *J Allergy Clin Immunol*. 2015;136(6):1532–1540.
- Philpott CM, Erskine S, Hopkins C, et al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK National Chronic Rhinosinusitis Epidemiology Study. *Respir Res*. 2018;19(1):129.
- Cody DT, Bryan Neel H, Ferreiro JA, Roberts GD. Allergic fungal sinusitis: the Mayo Clinic experience. *Laryngoscope*. 1994;104(9):1074–1079.
- Rui T, Zhang HY. Aspirin induced asthma accompanied with allergic bronchopulmonary aspergillosis: a case report. *Chin Med J*. 2010;123(17):2489–2492.
- Promsopa C, Kansara S, Citardi MJ, Fakhri S, Porter P, Luong A. Prevalence of confirmed asthma varies in chronic rhinosinusitis subtypes. *Int Forum Allergy Rhinol*. 2016;6(4):373–377.
- Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope*. 2009;119(9):1809–1818.
- Noverr MC, Toews GB, Huffnagle GB. Production of prostaglandins and leukotrienes by pathogenic fungi. *Infect Immun*. 2002;70(1):400–402.
- Cahill KN, Boyce JA. Aspirin-exacerbated respiratory disease: mediators and mechanisms of a clinical disease. *J Allergy and Clin Immunol*. 2017;139(3):764–766.

20. Loftus PA, Wise SK. Allergic fungal rhinosinusitis: the latest in diagnosis and management. In: Woodworth BA, Poetker DM, Reh DD, eds. *Rhinosinusitis With Nasal Polyposis. Advances in Otorhinolaryngology*. Vol. 79. Basel, Switzerland: Karger Publishers; 2016:13–20.
21. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res*. 2011;3(1):3–10.
22. Ferguson BJ, Barnes L, Bernstein JM, et al. Geographic variation in allergic fungal rhinosinusitis. *Otolaryngol Clin North Am*. 2000;33(2):441–449.