ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Allergic fungal rhinosinusitis – case series and literature review

Rinossinusite fúngica alérgica – série de casos e revisão da literatura

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ABSTRACT

Allergic fungal rhinosinusitis is a noninvasive subtype of chronic rhinosinusitis with nasal polyps associated with type 2 inflammation. It is characterized by immunoglobulin E-mediated fungal sensitization, the presence of allergic mucin, and typical computed tomography and magnetic resonance imaging findings in paranasal sinuses. Diagnosis is classically established using the Bent & Kuhn criteria; however, recent studies have indicated a lack of specificity for some of the major criteria. Treatment almost always requires surgery, and adjunctive therapy mainly consists of oral and/or topical corticosteroids. Omalizumab, dupilumab, and mepolizumab are currently approved for the treatment of chronic rhinosinusitis with nasal polyps in general, but clinical trials with these biologics have not included patients with allergic fungal rhinosinusitis. Here, we describe the main characteristics of patients diagnosed with allergic fungal rhinosinusitis treated in a university hospital, along with a literature review of published data.

Keywords: Sinusitis, allergic fungal sinusitis, respiratory hypersensitivity, biological products.

RESUMO

A rinossinusite fúngica alérgica é um subtipo não invasivo de rinossinusite crônica com pólipos nasais com inflamação do tipo 2. É caracterizada por sensibilização a fungos IgE mediada, mucina alérgica e achados característicos de tomografia computadorizada e ressonância magnética nos seios paranasais. O diagnóstico é classicamente feito usando os critérios de Bent & Kuhn. No entanto, estudos recentes indicaram a falta de especificidade de alguns critérios importantes. O tratamento na maioria das vezes é cirúrgico, e a terapia adjuvante consiste principalmente no uso de esteroides orais e/ou tópicos. O omalizumabe, dupilumabe e mepolizumabe estão atualmente aprovados para o tratamento da rinossinusite crônica com pólipos nasais em geral, mas os ensaios clínicos até o momento com esses produtos biológicos não envolveram pacientes com rinossinusite fúngica alérgica. Descrevemos as principais características dos pacientes diagnosticados com rinossinusite fúngica alérgica de um hospital universitário e revisamos os dados atuais da literatura sobre o tema.

Descritores: Sinusite, sinusite fúngica alérgica, hipersensibilidade respiratória, produtos biológicos.

Introduction

Allergic fungal rhinosinusitis (AFRS) is a noninvasive subtype of chronic rhinosinusitis with nasal polyps (CRSwNP) that typically develops in immunocompetent atopic individuals.[1,2] It is characterized by antifungal immunoglobulin E (IgE) sensitivity, eosinophil-rich mucus (allergic mucin), and characteristic findings on computed tomography (CT) and magnetic resonance imaging (MRI) of the paranasal sinuses.[2] AFRS occurs predominantly in geographic regions with warm and humid climates, which favor a higher environmental

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fungal burden.[1,3] The molecular pathways and immune responses in the pathophysiology of AFRS are still being elucidated. Dysfunction of the epithelial barrier and the presence of fungi within the sinus cavities can upregulate type 2 immune responses, leading to type I hypersensitivity, eosinophilic inflammation, and type 2 cytokine production.[1,4,5] The first description of AFRS as a distinct clinical entity was published in 1976 by Safirstein, who reported the case of a 24-year-old patient presenting with recurrent nasal obstruction, nasal polyps, thick secretions within the nose, and sinus cultures positive for *Aspergillus* species.[6] Since then, this condition has been increasingly investigated, and several studies are published annually to better understand its mechanisms. Diagnosis is based on the criteria defined by Bent and Kuhn.[7] Treatment of AFRS almost always requires surgical debridement of the affected sinuses combined with topical and oral corticosteroids, which reduce postoperative recurrence.[5,6,8] Biologic agents appear to be a promising option; however, more studies are required.[1,3-5,8,9] The objective of this study was to describe the main clinical characteristics of patients diagnosed with AFRS and followed in the chronic rhinosinusitis (CRS) outpatient clinics of the Immunology and Otorhinolaryngology Services of the Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ), in Rio de Janeiro, Brazil, and to review the current literature to support a better understanding of this condition.

Methods

A retrospective cross-sectional study was conducted based on a review of the medical records of patients with AFRS. Demographic characteristics, comorbidities, and laboratory findings were described, in addition to a review of the current literature on AFRS.

Results

A total of 5 patients with AFRS were included, 3 men and 2 women. The median age was 44 years (range, 12-54 years). Associated comorbidities included allergic rhinitis (n=2), arterial hypertension (n=2), type 2 diabetes (n=2), asthma (n=1), thyroid nodule (n=1), obesity (n=1), and gastroesophageal reflux disease (n=1). Mean total serum IgE level was 1419.5 IU/mL. All patients demonstrated sensitization to at least one fungus: *A. fumigatus* (n=4), *C. albicans* (n=3), *C. herbarum* (n=3), and *P. notatum* (n=1). Sensitization to other aeroallergens was also observed: *B. tropicalis* (n=3), *D. pteronyssinus* (n=3), *D. farinae* (n=3), and staphylococcal enterotoxins (n=2). The most common CT findings were expansile changes with thinning of bony structures. Regarding fungal cultures, only 2 patients had positive results, with *Aspergillus sp.* and *Curvularia sp.* identified. In 1 patient, direct mycological examination revealed numerous hyaline, septate, and branched hyphae and round, pigmented conidia (Table 1).

Review of the literature

The incidence of AFRS appears to be influenced by geographic factors, as most reported cases occur in regions with temperate climates and relatively high humidity.[1,3] Studies have shown that AFRS primarily affects men between 21 and 33 years of age, an age range significantly younger than that observed in patients with CRS without nasal polyps and CRSwNP.[10,11] The incidence of AFRS has been estimated to range from 1.3% to 10% of all patients with CRS undergoing surgery.[5,12] The most commonly affected sinuses include the ethmoid sinuses (71%-92%), maxillary sinuses (7%-76%), sphenoid sinuses (58%-86%), and frontal sinuses (29%-65%).[3] The most common fungi involved are dematiaceous fungi (*Bipolaris*, *Curvularia*, and *Exserohilum*) and *Aspergillus*, a hyaline mold.[13]

In this study, we identified several comorbidities, including allergic rhinitis and asthma. Previous reports indicate that up to 24% of patients with AFRS also have asthma.[4]

AFRS has a complex and not yet fully defined pathogenesis. The most established mechanism is an exaggerated type 2 inflammatory response. Additional contributing factors include bacterial colonization and superantigen expression, the direct effects of pathogenic fungi, and epithelial barrier dysfunction.[2,4,5] Activation of T helper 2 (Th2) cells leads to the release of interleukin (IL)-4, IL-5, and IL-13, which promote B-cell differentiation, IgE production, mast cell degranulation, and eosinophilia, resulting in elevated IgE, eosinophilic mucin, and fungal hypersensitivity.[2,4] *Staphylococcus aureus* is a common colonizer of the nasal cavities and has been shown to coexist with fungi within eosinophilic mucin in patients. With superantigen expression, *S. aureus* can amplify fungal-induced Th2 activation, contributing to the elevated total serum IgE levels characteristic of AFRS.[4,14] Environmental exposure

to fungal spores can facilitate their germination into immunogenic fungal hyphae within the sinus cavities, leading to epithelial barrier cell dysfunction and the release of epithelial-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin.[4,5,15] This triggers compensatory overstimulation of the type 2 immune response, with the ensuing inflammatory cascade driving eosinophilia, nasal polyposis, and mucus production. Mucosal swelling and mucin can trap additional fungal material, perpetually stimulating the dysfunctional response in a vicious cycle that clinically manifests as AFRS.[4]

Patients with AFRS typically present with nasal obstruction secondary to nasal polyposis, along with complaints of hyposmia or anosmia.[4,5] The mucin has a thick consistency often described as "peanut-butter-like," with its color varying from light tan to brown.[1,2,5] The affected nasal sinuses often undergo expansile changes that may lead to erosion of bony boundaries. In some individuals, these changes become sufficiently pronounced to result in orbital or facial deformities.[4]

In 1994, Bent and Kuhn established a set of major and minor criteria for the diagnosis of AFRS that remain in use today. The major criteria include: (1) type I hypersensitivity to fungi confirmed by history, skin testing, or serology; (2) nasal polyposis; (3) characteristic CT findings; (4) eosinophilic mucin

Table 1
Clinical and laboratory characteristics of patients with AFRS from the Immunology and Otorhinolaryngology Services of the Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ) , Rio de Janeiro, Brazil

Patient	Sex	Age, y	Comorbidities	Total IgE	Positive specific IgE	Culture
1	M	34	Thyroid nodule	2540	*B. tropicalis*, *A. fumigatus*, *P. notatum*, Staphylococcal enterotoxins	*Aspergillus sp.*
2	M	12	Allergic rhinitis	1963	*D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *A. fumigatus*, *C. albicans*, *C. herbarum*	*Curvularia sp.*
3	F	44	Diabetes Hypertension	726	*D. pteronyssinus*, *D. farinae*, *A. fumigatus*, *C. albicans*, *C. herbarum*, Staphylococcal enterotoxins	Negative
4	M	45	Asthma	449	*D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *A. fumigatus*	Negative
5	F	54	Obesity, allergic rhinitis, GERD, diabetes, hypertension	NA	*C. albicans*, *C. herbarum*	Direct mycological examination: numerous hyaline, septate, and branched hyphae and round, pigmented conidia

A. fumigatus: Aspergillus fumigatus; *B. tropicalis: Blomia tropicalis*; *C. albicans: Candida albicans*; *C. herbarum: Cladosporium herbarum*; *D. farinae: Dermatophagoide farinae*; *D. pteronyssinus: Dermatophagoide pteronyssinus*; GERD: gastroesophageal reflux disease; NA: not available (test not performed); *P. notatum: Penicillium notatum*.

without fungal invasion of sinus tissue; and (5) a positive fungal stain of sinus contents removed during surgery. Minor criteria include: (1) bone erosion on radiography; (2) positive fungal cultures; (3) unilateral predominance of disease; (4) Charcot-Leyden crystals; and (5) peripheral eosinophilia. For diagnosis, all five major criteria must be fulfilled.[1,4,5,7,8] However, these diagnostic criteria require reassessment, as several inconsistencies with clinical findings have been reported.[4]

IgE-mediated hypersensitivity to fungi is very common in AFRS, with *A. fumigatus* being the most frequent antigen, as seen in our case series.[4,9]

Radiologic evaluation typically includes radiography of the paranasal sinus, CT, and MRI. Findings can help identify nasal polyps, the extent of disease, bony expansion, and erosive changes. As observed in our cohort, expansile changes with thinning of bony structures are common. CT imaging of the nasal sinuses in patients with AFRS typically shows near complete opacification with heterogenous radiodensity of the soft tissue of the sinuses.[1,2,5,17] More than 30% of patients with AFRS have skull-base or orbital expansion or erosion that is extensive enough to cause local anatomic distortion (including the orbital and cranial cavities) and visual disturbances.[1] MRI is highly valuable for assessing soft tissue extension, orbital pathology, and intracranial involvement.[2,16,17]

As first described by Millar et al., Lamb et al., and Katzenstein et al., histologic examination of allergic mucin shows characteristic findings. Branching, noninvasive fungal hyphae are observed surrounding layers of eosinophils and Charcot-Leyden crystals. H&E staining is typically complemented by Gomori methenamine silver staining to better identify fungi.[18-20] Fungal cultures obtained from allergic mucin may provide supportive evidence in the evaluation of AFRS; however, their results must be interpreted with caution. It is important to emphasize that a diagnosis cannot be confirmed or excluded solely on the basis of culture findings, since a positive culture may simply represent saprophytic fungal growth.[4,21]

In the management of AFRS, surgery combined with topical and oral corticosteroids remains the standard of care. Endoscopic sinus surgery allows removal of nasal polyps and eosinophilic mucin, which harbors the fungi responsible for triggering and perpetuating sinonasal inflammation. It also improves drainage and ventilation of the affected sinuses, thereby increasing the penetration of topical medications postoperatively.[1,2,4,8,9,15]

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020), systemic corticosteroids improve short-term postoperative outcomes and reduce long-term recurrence of AFRS.[12] However, their use should be limited to short courses due to the risk of adverse effects. Topical corticosteroids are also a key component of AFRS therapy and are essential for maintenance treatment, offering the advantages of minimal systemic absorption and low rates of adverse events.[3,4,12] Nonstandard, off-label topical steroid therapy, such as high-volume budesonide sinonasal irrigation, may provide higher steroid concentrations to the sinonasal mucosa depending on the mode of delivery.[22]

Currently, omalizumab, dupilumab, and mepolizumab are approved for the treatment of CRSwNP; however, patients with AFRS were excluded from those trials.[1,4,5,8] These biologic agents target type 2 inflammatory mediators: IgE, IL-4, IL-5, and IL-13.[8] Dupilumab inhibits signaling of both IL-4 and IL-13 and is currently being evaluated in phase III clinical trials for AFRS (NCT04684524).[4,8] Biologic agents appear to be a promising option, but more studies are required.[1,3-5,8,9]

Because AFRS is characterized by type I hypersensitivity to fungi, immunotherapy has been proposed as a potential strategy to attenuate the immune response to fungi and reduce disease burden.[1,15] However, to date, the only systematic review examining immunotherapy in AFRS found insufficient evidence to recommend for or against its use, due to methodological limitations such as small sample sizes, adjunctive use of other treatments, and lack of standardized control groups.[5] EPOS2020 describes immunotherapy as an adjunctive option that may reduce symptoms and the need for revision surgery.[3,12] Due to the limited number of published studies, immunotherapy is currently regarded as an adjunctive therapy.[5,23]

Topical antifungals have shown inconsistent activity and limited ability to access all affected mucosa, even in surgically opened sinus cavities. Regarding oral antifungals, most clinical trials have demonstrated limited treatment benefit.[4] A Cochrane review concluded that topical and oral antifungals in patients with any CRS phenotype did not demonstrate any clinical benefit.[1,2,4,24]

Conclusion

Our findings provide an updated account of AFRS cases followed in our center. It is important to consider this diagnosis in immunocompetent patients with CRSwNP who present with bilateral expansile changes and characteristic allergic mucin. In addition, we highlight the need to reevaluate the currently used diagnostic criteria, representing a potential area for future research.

References

1. Luong AU, Chua A, Alim BM, Olsson P, Javer A. Allergic Fungal Rhinosinusitis: The Role and Expectations of Biologics. J Allergy Clin Immunol Pract. 2022 Dec;10(12):3156-62.
2. Dykewicz MS, Rodrigues JM, Slavin RG. Allergic fungal rhinosinusitis. J Allergy Clin Immunol. 2018 Aug;142(2):341-51.
3. Kokoszka M, Stryjewska-Makuch G, Kantczak A, Górny D, Glück J. Allergic Fungal Rhinosinusitis in Europe: Literature Review and Own Experience. Int Arch Allergy Immunol. 2023;184(9):856-65.
4. Chua AJ, Jafar A, Luong AU. Update on Allergic Fungal Rhinosinusitis. Ann Allergy Asthma Immunol. 2023;S1081-1206(23)00126-6.
5. Suzuki M, Connell J, Psaltis AJ. Pediatric allergic fungal rhinosinusitis: optimizing outcomes. Curr Opin Otolaryngol Head Neck Surg. 2021;29:510-16.
6. Safirstein BH. Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. Chest. 1976 Dec;70(6):788-90.
7. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994 Nov;111(5):580-8.
8. Cameron BH, Luong AU. New Developments in Allergic Fungal Rhinosinusitis Pathophysiology and Treatment. Am J Rhinol Allergy. 2023;37:214-20.
9. Nakayama T, Miyata J, Inoue N, Ueki S. Allergic fungal rhinosinusitis: What we can learn from allergic bronchopulmonary mycosis. Allergol Int. 2023 Oct;72(4):521-9.
10. Xu T, Guo XT, Zhou YC, Zhou Q, Wang YF. Consideration of the Clinical Diagnosis of Allergic Fungal Sinusitis: A Single-Center Retrospective Study. Ear Nose Throat J. 2023 Apr 5:1455613231167247.
11. Lu-Myers Y, Deal AM, Miller JD, Thorp BD, Sreenath SB, McClurg SM, et al. Comparison of Socioeconomic and Demographic Factors in Patients with Chronic Rhinosinusitis and Allergic Fungal Rhinosinusitis. Otolaryngol Head Neck Surg. 2015 Jul;153(1):137-43.
12. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600.
13. Park MJ, Han JY. Allergic Mucin in Allergic Fungal Rhinosinusitis. J Allergy Clin Immunol Pract. 2023 Aug;11(8):2574-5.
14. Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis-more than a fungal disease? J Allergy Clin Immunol. 2013 Aug;132(2):487-9.e1.
15. Tyler MA, Luong AU. Current understanding of allergic fungal rhinosinusitis. World J Otorhinolaryngol Head Neck Surg. 2018;4:179-85.
16. Desa C, Tiwari M, Pednekar S, Basuroy S, Rajadhyaksha A, Savoiverekar S. Etiology and Complications of Deep Neck Space Infections: A Hospital Based Retrospective Study. Indian J Otolaryngol Head Neck Surg. 2023 Jun;75(2):697-706.
17. Raghvi A, Priya K, Balaji D. Varied Clinical Presentations of Allergic Fungal Rhinosinusitis-A Case Series. Indian J Otolaryngol Head Neck Surg. 2023 Jun;75(2):571-8.
18. Millar JW, Johnston A, Lamb D. Allergic bronchopulmonary aspergillosis of the maxillary sinuses [abstract]. Thorax. 1981;36:710.
19. Lamb D, Millar J, Johnston A. Allergic aspergillosis of the paranasal sinuses. J Pathol. 1982,137:56.
20. Katzenstin A, Greenberger P, Sale S. Allergic aspergillus sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol. 1983,72:89-93.
21. Luong A, Marple BF. Update on Allergic Fungal Rhinosinusitis. Current Fungal Infection Reports. 2007;1:12-8.
22. Marglani OA, Simsim RF. Emerging Therapies in the Medical Management of Allergic Fungal Rhinosinusitis. Indian J Otolaryngol Head Neck Surg. 2024 Feb;76(1):277-87.
23. Patadia MO, Welch KC. Role of immunotherapy in allergic fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2015 Feb;23(1):21-8.
24. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev. 2011;(8):CD008263.

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