

The prevalence of allergic fungal rhinosinusitis in sinonasal polyposis

Mehdi Bakhshaei · Mohammad Fereidouni ·
Morteza Nourollahian Mohajer · Mohammad Reza Majidi ·
Farahzad Jabbari Azad · Toktam Moghiman

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Abstract Allergic fungal sinusitis (AFS) is a noninvasive form of fungal rhinosinusitis with a prevalence of 6–9 % among all rhinosinusitis cases requiring surgery. The fungi causing AFRS have a great diversity and regional variation in the incidence of AFS has been reported worldwide. The aim of this study was to evaluate the prevalence of AFS among rhinosinusitis patients in the north east of Iran. In a prospective cross-sectional study 127 patients with sinonasal polyposis who were candidates for surgery were recruited. All cases were evaluated by sinonasal CT scan, Prick test for common regional allergens, total serum immunoglobulin E (IgE) level, and allergic mucin culture for fungi in suspected cases. Data analyses were done using

SPSS version 13.0. Their mean age was 37.4 ± 11.6 years, the male-to-female ratio was 69/58. Eleven patients (9.45 %) met the AFS criteria. Nine cases had a positive culture for *Aspergillus* specimen and three for *Alternaria*. Prick test was positive for at least one allergen in 28 cases (22.05 %). The most common allergen was weed. The total IgE level was significantly higher in AFS patients. This study showed the prevalence of AFS among patients with nasal polyposis to be 9.45 %.

Keywords Allergy · Allergic fungal sinusitis · *Aspergillus* · Nasal polyp · Rhinosinusitis

M. Bakhshaei · M. N. Mohajer
Ear, Nose and Throat Research Center, Imam Reza Hospital,
Faculty of Medicine, Mashhad University of Medical Sciences,
Mashhad, Iran

M. Fereidouni
Asthma, Allergy and Immunology Research Center, Faculty of
Medicine, Birjand University of Medical Sciences, Birjand, Iran

M. R. Majidi
Department of Otorhinolaryngology, Ear, Nose and Throat
surgery, Qaem Hospital, Mashhad University of Medical
Sciences, Mashhad, Iran

F. J. Azad
Department of Clinical Allergy and Immunology, Allergy
Research Center, Faculty of Medicine, Mashhad University
of Medical Sciences, Mashhad, Iran

T. Moghiman (✉)
Allergy Research Center, Qaem Hospital, School
of Medicine, Mashhad University of Medical Sciences,
9176699199, Mashhad, Iran
e-mail: T_moghiman@yahoo.co.uk; Moghimant1@mums.ac.ir

Introduction

Allergic fungal rhinosinusitis (AFRS) was first reported as a distinct clinical disorder in 1976 [1]. AFRS is a truly unique pathologic entity, defined largely by the presence of allergic fungal mucin, which is a thick, tenacious, eosinophilic secretion with characteristic histologic findings [2]. In 1994, Bent and Kuhn [3] published their diagnostic criteria focusing on the histologic, radiographic, and immunologic characteristics of the disease including type I hypersensitivity, nasal polyposis, characteristic findings on CT scan, presence of fungi on direct microscopy or culture, and allergic mucin containing fungal elements without tissue invasion.

Maxillary sinus rhinosinusitis due to *Aspergillus* was described by Millar and Katzenstein in 1981 and 1983 respectively, who described the presence of groups of necrotic eosinophils, Charcot-Leyden crystals and noninvasive fungal hyphae in the sinus mucin of patients with chronic sinusitis [4]—calling this “allergic rhinosinusitis due to *Aspergillus*”.

Although recent studies demonstrated that there are potential deficits in the innate and acquired immunity of CRS patients that might reduce their ability to react to fungi, there are a few studies that suggest a causative role of fungi in CRS, though they might have a disease-modifying role.

Almost a decade after Ponikau hypothesis, there is no convincing evidence for clinical improvement of CRS with anti-fungal therapy. It means that currently the key role of fungi in a majority of the CRS cases is questionable and anti-fungal treatment should not be used routinely [5].

Asero et al. [6] found patients with polyposis to exhibit fungal sensitization, particularly to *Candida albicans*, although it was a controversial genus [7]. In a study of patients with chronic rhinosinusitis, Ponikau et al. [8] detected fungi in 96 % of nasal secretion cultures and identified 40 different fungal species in the nasal sinuses. According to these studies, the condition is mediated by IgE in response to different fungi present in the sinonasal eosinophilic mucin. The theory is supported by the observation of specific IgE in cultures. Currently, the most widely accepted hypothesis excludes the allergic etiology and proposes the term “eosinophilic fungal sinusitis” [8, 9].

The fungi causing AFRS have a great diversity. Manning and Holman [10] in 1998 reported 168 positive cultures, 87 % of the cases showed dematiaceous fungi, and 13 % showed *Aspergillus* species. Interestingly, in the Indian scenario *A. flavus* was isolated in more than 80 % of the cases of AFRS [11–15]. *A. flavus* was also isolated from 50 % of patients diagnosed with AFRS in the Middle East [16]. Telmesani [17] reported a 12 % prevalence of AFS among sinonasal polyposis in Saudi Arabia in which *Aspergillosis* was found in 72 % of the cases while the rest had a negative culture.

Regional variation in the incidence of AFRS has been reported worldwide. The aim of this study was to evaluate the prevalence of AFRS among rhinosinusitis patients in the north east of Iran and the common fungi related to this disorder.

Materials and methods

In a prospective cross-sectional study From December 2006 to November 2010, 127 patients with over a 1-year-history of sinonasal polyposis who were candidates for surgical intervention were recruited. They were selected from the patients being referred to the Ear, Nose and Throat clinics of two main educational hospital of Mashhad, Iran (Qaem and Imam Reza Hospitals) with the diagnosis of unilateral or bilateral nasal polyps for undergoing functional endoscopic sinus surgery (FESS).

Intractable sinonasal polyposis was the main criteria for surgery. The outcome measures were age, sex, CT scan findings, IgE level, operative details and atopy. The final diagnosis was based on histopathological findings of the tissue and mucin, recurrence rate in patients followed up for 1 year or more, the presence of associated asthma, and the results of fungal cultures in suspected cases of AFS.

Skin prick test was performed with a battery of 13 common regional allergens' extracts (Hollister-Stier, USA) including molds, mites, cockroaches, weeds and trees. Testing method was previously described [18].

CT scan staging of nasal polyps was based on the staging of Lund Mccay [19]. AFS was taken into consideration if the histopathology confirmed the presence of eosinophilic mucin containing hyphae.

Data analyses were done using SPSS version 13.0 statistical software (SPSS Inc, Chicago, IL). For comparisons, the *t* test for independent variables, analysis of variance and Chi-square tests were used wherever required. The difference was considered as significant if $P < 0.05$.

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences and it conforms to the provisions of the Declaration of Helsinki. All patients were fully informed of the study protocol and gave an informed consent prior to study entrance.

Results

A total of 127 patients with sinonasal polyposis who were candidates for endoscopic sinus surgery entered the study. Their mean age was 37.4 ± 11.6 years and the male-to-female ratio 69/58. Twelve (9.45 %) met the AFS criteria while the remaining 115 patients showed histopathological features of chronic hyperplastic rhinosinusitis.

CT scan staging was performed for all patients; the mean score according to Lund Mackay was 13.48 and 18.90 for none AFS and AFS cases, respectively. This difference was statistically significant ($P < 0.05$).

87 patients were followed up for 1 year or more with a mean duration of 16 months. The overall recurrence rate in these patients was 19.54 % (17 cases). Among the AFS patients nine were followed up for 2 years for which recurrence was detected in four cases (44.44 %) whom underwent endoscopic surgery once again.

105 patients were non-asthmatic whereas 22 patients (20.95 %) had a positive history for asthma. Only two patients with AFS had an associated asthma. Smoking habits were found in 13 (10.24 %) while all smokers were male.

Prick test was positive for at least one allergen in 28 cases (22.05 %). The most common allergen was weed. A positive prick test for *Alternaria* and *Aspergillosis* were

Table 1 The most common allergens among patients with Allergic Fungal Sinusitis

	Allergens	Number	Percent
1	Dermatophogoidesfarinae	17	13.4
2	Dermatophogoidespteronysinus	13	10.2
3	Alternariaalternata	14	11.0
4	Aspergillus mix	13	10.2
5	Moulds yeasts mix	12	9.4
6	Cockroach	15	11.8
7	Rough pigweed (Amaranthusretroflexus)	24	18.9
8	Bermuda grass (cynodondactylon)	14	11.0
9	Fat hen (Chenopodium album)	32	25.2
10	Sorrel (Rumexacetosa)	11	8.7
11	Kochia weed	26	20.5
12	Russian thistle (Salsola kali)	31	24.4
13	Ash (Fraxinus excelsior)	5	3.9
	Overall Mites	20	15.75
	Overall Fungi	17	13.39
	Overall Weeds	41	32.28

The extract includes Alternaria t, Hormodendrum c, Phoma h, Helminthosporium I, Aspergillus mix, Penicillium mix, Fusarium v, Rhizopus n

found in 11(8.66 %) and 10(7.87 %) cases, respectively (Table 1).

In 8 of the 12 cases of AFS, Aspergillus species were demonstrated in fungal cultures. In the remaining three, Alternaria was seen on culture.

The total IgE level among patients with polyposis alone was 207.45 while the same value was 520.14 in AFS cases. This difference was statistically significant ($P < 0.05$).

Discussion

Nasal polyps are a common problem with different etiologies. It has always been an issue of importance to estimate the incidence of AFS among patients with nasal polyps. In this prospective study we collected data from the medical records of 91 patients admitted with the preoperative diagnosis of nasal polyps in a period of about 4 years for endoscopic sinus surgery. A valid diagnosis was revealed in the medical records of 127 patients based on histopathologic studies whereas 12 (9.45 %) cases were proven to have AFS.

In 2005, BeepSee et al. reported that in adult Malaysian patients with refractory rhinosinusitis the incidence of AFS was 26.7 %. The presence of allergic mucin was the diagnosing tool for AFS, by which they found fungus in the secretions of only 5 patients (16.7 %) and in nasal secretions and surgical specimens of 11 (36.7 %) others [19]. Braun et al. [20] in 2003 reported a 7 % incidence of AFS

among nasal polyposis patients. In another study in Saudi Arabia by Telmesani [17] the prevalence of AFRS among patients with nasal polyposis was reported as 12.1 % and there was a highly significant statistical difference in IgE levels between patients suffering from AFRS and chronic hyperplastic rhinosinusitis with nasal polyps. This variability in incidence might be the result of different diagnostic techniques used or due to differences in its geographical distribution.

The total IgE level in our study was significantly higher in AFS patients in comparison to those with chronic rhinosinusitis. These results are in accordance with those of Ferguson's study stating that total IgE in patients with AFS is frequently elevated with a mean of 668 IU/mL and the normal concentration being less than 125 IU/mL [21]. In addition, in a study conducted by Schubert [21], it was shown that the total IgE level had a significant correlation with the disease severity, and that a 10 % or more increase in total serum IgE during the follow-up period was a strong predictor of recurrence and the need for surgical intervention.

Although it is believed that total IgE is an important factor in the diagnosis and prognosis of AFRS, the large standard deviation made it difficult to be used as a diagnostic tool. This marked variability could to some extent be attributed to fluctuation in the disease activity. Still, total IgE may be helpful in differentiating between eosinophilic mucin rhinosinusitis and AFS, where it is elevated in AFS cases [22].

In the present study, the overall recurrence rate for nasal polyps was 19.54 % (out of 87 patients). Four of the nine (44.44 %) cases with AFS showed recurrence during the first year, while the recurrence rate in those with hyperplastic rhinosinusitis was 16.67 % (13 patients). The difference was statistically insignificant. Wynn and Har [23] in a retrospective study, found a recurrence rate of 60 % in patients with nasal polyps after 40 months of follow-up. The lower recurrence rate in our study could be due to the shorter follow-up period. No exact figure for the recurrence rate of AFS was found in the literature. When applying the grading system for nasal polyps described by Lildholdt et al. [24], a significant increase in the rate of recurrence was found with the increase in grade. Therefore this grading system could be used as a prediction index for the recurrence of nasal polyps.

In the current study asthma was found to be associated with nasal polyps in 25 cases (27.5 %) and only in two patient with AFS (16.67 %), showing that asthma is not a major associated pathology in allergic fungal sinusitis. The rate of associated asthma in AFS cases ranges from 30–40 % in most of the available literature. The lower incidence of this condition in our study may in part be due to the fewer studied patients for which an accurate

incidence of associated asthma could not be obtained. If asthma is not considered as an important associated pathology, the high incidence of associated asthma in the literature could be related to the combination of AFS and non-fungal eosinophilic mucin rhinosinusitis in which the incidence rate of associated asthma is 93 % [25].

In nine of the twelve cases diagnosed as AFS, *Aspergillus* was the only revealed species. These findings are in agreement with the results of Ferguson et al. noting that a geographical variability may be present in the incidence of AFS and fungal species associated with the disease process. Dematiaceous fungi are most common in the United States whereas *Aspergillus* species are mostly reported in the Middle East [17, 26]. From this study, a conclusion can be drawn indicating that the prevalence of AFS among patients with nasal polyps is 9.45 %, and the IgE level in patients with AFS is higher than those with chronic hyperplastic rhinosinusitis. This suggests that for prognosing the rate of disease recurrence, CT grading of nasal polyps can be useful and that no significant association exists between asthma and nasal polyps.

AFS represents a distinct type of fungal RS. Adherence to strict diagnostic criteria is required because it can be confused with other forms of fungal RS and other types of hypertrophic sinus diseases (HSD).

Proper diagnosis is essential for planning treatment and follow-up. Similarities and differences have been described between AFS and other forms of HSD and ABPA (allergic bronchopulmonary aspergillosis). Recent advances in our understanding of the immunopathology of AFS have drawn comparisons with other chronic inflammatory diseases. Future AFS, HSD, and ABPA research may provide additional insight into the mechanisms of not only other common chronic inflammatory respiratory tract diseases but of those of other organ systems as well.

Conflict of interest None.

References

1. Safirstein B (1976) Allergic bronchopulmonary aspergillosis with obstruction of the upper respiratory tract. *Chest* 70:788–790
2. Glass D, Amedee RG (2011) Allergic fungal rhinosinusitis: a review. *Ochsner J* 11(3):271–275
3. Bent JP 3rd, Kuhn FA (1994) Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 111(5):580–588
4. Katzenstein AL, Sale SR, Greenberger PA (1983) Allergic *Aspergillus* sinusitis: a newly recognized form of sinusitis. *J Allergy Clin Immunol* 72(1):89–93
5. Fokkens WJ, van Drunen C, Georgalas C, Ebbens F (2012) Role of fungi in pathogenesis of chronic rhinosinusitis: the hypothesis rejected. *Curr Opin Otolaryngol Head Neck Surg* 20(1):19–23
6. Asero R, Bottazi G (2000) Hypersensitivity to molds in patients with nasal polyposis: a clinical study. *J Allergy Clin Immunol* 105:186–188
7. Solomon WR (1999) Pollens and fungi. In: Allergy ME (ed) *Principles and practice*, vol 3. Mosby, Philadelphia, pp 469–514
8. Ponikau H, Sherris D, Kern E, Homburger H, Frigas E, Gaffey T, Roberts G (1999) The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc* 74:877–884
9. Stammberger H (1999) Examination and endoscopy of the nose and paranasal sinuses. In: Mygind N, Lildholt T (eds) *Nasal polyposis. An inflammatory disease and its treatment*. Munksgaard, Copenhagen, pp 120–36
10. Manning SC, Holman M (1998) Further evidence for allergic pathophysiology in allergic fungal sinusitis. *Laryngoscope* 108(10):1485–1496
11. Chakrabarti A, Sharma SC, Chandler J (1992) Epidemiology and pathogenesis of paranasal sinus mycoses. *Otolaryngol Head Neck Surg* 107(6 Pt 1):745–750
12. Saravanan K, Panda NK, Chakrabarti A, Das A, Bapuraj RJ (2006) Allergic fungal rhinosinusitis: an attempt to resolve the diagnostic dilemma. *Arch Otolaryngol Head Neck Surg* 132(2):173–178
13. Chhabra A, Handa KK, Chakrabarti A, Mann SB, Panda N (1996) Allergic fungal sinusitis: clinicopathological characteristics. *Mycoses* 39(11–12):437–441
14. Panda NK, Sharma SC, Chakrabarti A, Mann SB (1998) Paranasal sinus mycoses in north India. *Mycoses* 41(7–8):281–286
15. Dhiwakar M, Thakar A, Bahadur S et al (2003) Preoperative diagnosis of allergic fungal sinusitis. *Laryngoscope* 113(4):688–694
16. Taj-Aldeen SJ, Hilal AA, Schell WA (2004) Allergic fungal rhinosinusitis: a report of 8 cases. *Am J Otolaryngol* 25(3):213–218
17. Telmesani LM (2009) Prevalence of allergic fungal sinusitis among patients with nasal polyps. *Ann Saudi Med* 29(3):212–214
18. Fereidouni M, Hossini RF, Azad FJ, Assarehzadegan MA, Varasteh A (2009) Skin prick test reactivity to common aeroallergens among allergic rhinitis patients in Iran. *Allergol Immunopathol (Madr)* 37(2):73–79
19. Goh BS, Gendeh BS, Rose IM, Pit S, Samad SA (2005) Prevalence of allergic fungal sinusitis in refractory chronic rhinosinusitis in adult Malaysians. *Otolaryngol Head Neck Surg* 133(1):27–31
20. Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H (2003) ‘Eosinophilic fungal rhinosinusitis’: a common disorder in Europe? *Laryngoscope* 113(2):264–269
21. Schubert MS (2004) Allergic fungal sinusitis: pathogenesis and management strategies. *Drugs* 64(4):363–374
22. Ryan MW, Marple BF (2007) Allergic fungal rhinosinusitis: diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg* 15(1):18–22
23. Wynn R, Har-El G (2004) Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. *Laryngoscope* 114(5):811–813
24. Lildholdt T, Rundcrantz H, Bende M, Larsen K (1997) Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. *Arch Otolaryngol Head Neck Surg* 123(6):595–600
25. Ferguson BJ (2000) Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. *Laryngoscope* 110(5 Pt 1):799–813
26. Ferguson BJ, Barnes L, Bernstein JM et al (2000) Geographic variation in allergic fungal rhinosinusitis. *Otolaryngol Clin North Am* 33(2):441–449