RHINOLOGY

Comparison of the clinical characteristics of bilateral and unilateral fungal balls in Korea

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Abstract

Objective Fungal rhinosinusitis occurs in different forms depending on race and region. While allergic fungal rhinosinusitis is common in Caucasians, fungal ball (FB) is more common in Asians. However, most cases are reported as unilateral, and clinical data on bilateral FB (BFB) are rare. Therefore, the purpose of this study was to analyze and to compare the clinical characteristics of BFB and unilateral FB (UFB) in Koreans.

Methods We retrospectively analyzed medical records and computed tomography (CT) images of 434 patients diagnosed with FB. The patients were divided into two groups: BFB and UFB. Demographic data, multiple allergen simultaneous test including total or specific immunoglobulin E (IgE) levels, symptoms, CT findings, treatment, and outcomes were analyzed.

Results Among the patients, 26 had BFB and 408 had UFB. Hypertension was noted in 61.5% of the BFB and 39% of the UBF individuals ($p = 0.023$). While total IgE levels were similar between the two groups, *Dermatophagoides pteronyssinus* ($p = 0.004$), *Cladosporium* ($p = 0.017$), and *Aspergillus*-specific IgE positivity ($p = 0.025$) were significantly higher in the BFB than in the UFB group. Not only symptoms such as postnasal drip ($p = 0.013$), mucopurulent rhinorrhea ($p = 0.009$), and foul odor ($p = 0.037$), but also sphenoid sinus involvement on CT images were more common in the BFB than in the UFB group ($p = 0.011$).

Conclusion Patients with BFB in Korea showed more common hypertension and symptoms of foul odor, mucopurulent rhinorrhea, and postnasal drip with allergy positivity compared to those with UFB. Therefore, understanding clinical characteristics of BFB will allow clinicians to approach BFB more appropriately.

Keywords Fungal rhinosinusitis · Bilateral · Fungal ball · *Aspergillus* · Korea

Introduction

Fungal rhinosinusitis (FRS) is a form of sinusitis wherein fungi are involved in the immunopathogenesis [1]. FRS occurs in about 10% of patients requiring nasal or sinus surgeries and is most commonly classified into non-invasive

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FRS and invasive FRS depending on the presence or absence of fungal hyphae in the tissues detected using microscopic examination [2]. In general, non-invasive FRS was classified as fungal ball (FB) or allergic fungal rhinosinusitis (AFRS) [3]. These can be classified histologically according to the presence of dense conglomerated fungal hyphae without tissue invasion [2] or eosinophilic mucin with inflammatory cells, Charcot-Leyden crystals, and branching non-invasive fungal hyphae [4]. Especially, FB is known to be the most common subtype of FRS, accounting for 53.2–72% of FRS [5]. Due to the development of imaging technologies, such as endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) as well as increased life expectancy, the incidence of FRS and FB have increased over the past several decades [5–7].

Interestingly, prevalence and incidence of FRS is known to differ not only ethnically but also regionally. It occurs commonly in the form of AFRS in Caucasians [8], while FB

is more common in Asians [9]. In addition, AFRS is more common in India, the Middle-East, and the southeastern parts of the United States, such as Alabama, Georgia, and Texas, which are hot and dry in climate [10–12]. Meanwhile, FB is common in France, Italy, Taiwan, and Korea [13–18]. However, FB mostly occurs unilaterally, and little is known about sinonasal FB in bilateral paranasal sinuses due to its rarity.

In addition, the incidence of unilateral fungal ball (UFB) has recently been reported to increase [19], and that of bilateral fungal ball (BFB) may follow similar tendency to UFB. Nevertheless, there have been a few reports of BFB in paranasal sinuses, only small numbers of BFB patients in these studies were included [9, 13, 20–22]. Additionally, studies on the clinical features of BFB and UFB are lacking. Therefore, the aim of this study was to analyze and compare the clinical characteristics of BFB and UFB in Korean patients.

Materials and methods

Study design

We retrospectively reviewed electronic medical charts including pathology reports and CT images for 434 FB patients between January 2008 and June 2018. All patients were finally diagnosed through postoperative histopathologic examination. FB was defined as an accumulation of dense conglomerated fungal hyphae in the sinuses without tissue invasion [2], and patients diagnosed with AFRS and invasive fungal rhinosinusitis were excluded. Especially, using the diagnostic criteria of AFRS described by Bent and Kuhn et al. [4] we defined AFRS as the presence of eosinophilic mucin with inflammatory cells, Charcot-Leyden crystals, and branching non-invasive fungal hyphae based on histologic findings. Periodic acid-Schiff staining or Grocott's methenamine silver staining was performed to confirm fungal hyphae in the tissues and identify individual species according to morphology, such as the angle of hyphae. The subjects were divided into two groups depending on where lesions were located: BFB versus UFB. Demographic data, underlying diseases including hypertension, diabetes mellitus, and autoimmune disease, symptoms, treatment, and outcomes, were investigated. The Korean version of the Sniffin' Sticks Test II was used to test for olfactory disorders [23]. Total and specific Immunoglobulin E (IgE) levels in all patients were measured by multiple allergen simultaneous tests (MAST), consisting of antigens such as house dust mites, fungi, tree pollens, and weed pollens. Cases of more than Class 2 (0.70 IU/ml) were considered to be positive for the antigen [24]. CT scans were evaluated by a radiologist using the impression of chronic rhinosinusitis rather than FRS. To evaluate differences in the anatomical variations of

the paranasal sinus between the two groups, the presence of septal deviation, concha bullosa, and Haller cells was examined. CT images were also used to identify the presence of calcifications or soft-tissue densities in the FB lesions and to examine the involved sinuses, including the ethmoid, maxillary, frontal, and sphenoid sinuses. In the case of BFB, the distribution of lesions on both sides was also evaluated.

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics for Windows Version 23.0 (IBM Corp., Armonk, NY, USA). Continuous data are presented as means ± standard deviations, while categorical data are presented as a percentage of the group total. Student's t tests were performed according to the results of a Kolmogorov–Smirnov test. Differences in categorical data between the two groups were compared using chi-square tests or Fisher's exact test. P values < 0.05 were considered statistically significant.

Results

Subject characteristics

The demographic data of the 434 FB patients included in this study are shown in Table 1. The BFB group comprised 26 (6.0%) patients, and the UFB group included 408 (94.0%). The mean age was $63.6 ± 12.5$ years in the BFB group and $60.2 ± 12.2$ years in the UFB group ($p = 0.174$). The BFB group included 18 (69.2%) women and the UFB group included 279 (68.4%) women ($p = 0.928$). The proportion of patients with hypertension was larger in the BFB group ($n = 16$, 61.5%) than in the UFB group ($n = 159$, 39.0%), a statistically significant difference ($p = 0.023$). However, no statistical difference was observed between the two groups in the incidence of diabetes mellitus or autoimmune disease. Among the revision cases, the incidence of BFB (3 cases, 11.5%) was higher than that of UFB (13 cases, 3.2%), but there was no statistically significant difference between the two groups ($p = 0.064$). Although total IgE positivity showed no statistical difference ($p = 0.54$), specific IgE levels for *Dermatophagoides pteronyssinus, Cladosporium,* and *Aspergillus* were significantly higher in the BFB group than in the UFB group ($p = 0.004$, $p = 0.017$, and $p = 0.023$, respectively). Results of KVSS II revealed no statistical intergroup differences.

Differences in symptomatology

Patient symptoms in the two groups are shown in Table 2. Three (11.5%) patients in the BFB group and 74 (18.1%) in the UFB group were diagnosed incidentally without any

Table 1 Demographic data

	BFB	UFB	P value
Total number of patients	26 (6.0)	408 (94.0)	
Age, years ± SD	63.6 ± 12.5	60.2 ± 12.2	0.174
Female, *n* (%)	18 (69.2)	279 (68.4)	0.928
Hypertension, *n* (%)	16 (61.5)	159 (39.0)	0.023*
Diabetes mellitus, *n* (%)	5 (19.2)	75 (18.4)	1
Autoimmune disease, *n* (%)	2 (7.7)	14 (3.4)	0.248
Revision cases, *n* (%)	3 (11.5)	13 (3.2)	0.064
MAST positive, *n* (%)	8 (32)	132 (38.2)	0.54
Dermatophagoides pteronyssinus, *n* (%)	8 (32)	34 (9.9)	0.004*
Dermatophagoides farinae, *n* (%)	4 (16)	57 (16.5)	1
House dust mite, *n* (%)	4 (16)	28 (8.1)	0.255
Cladosporium, *n* (%)	3 (12)	6 (1.7)	0.017*
Aspergillus, *n* (%)	3 (12)	11 (3.2)	0.025*
Alternaria, *n* (%)	0 (0)	3 (0.9)	1
Penicillium, *n* (%)	0 (0)	4 (1.2)	1
KVSS, *n* (%)	20 (76.9)	278 (68.1)	0.349
Normosmia, *n* (%)	5 (25)	99 (35.5)	0.342
Hyposmia, *n* (%)	7 (35)	98 (35.3)	0.982
Anosmia, *n* (%)	8 (40)	81 (29)	0.3

BFB Bilateral fungal ball, *UFB* unilateral fungal ball, *SD* standard deviation, *MAST* multiple allergen simultaneous tests, *KVSS* Korean Version of the Sniffin' Sticks Test

*$p < 0.05$

Table 2 Symptoms between the two groups

	BFB (*n* = 26)	UFB (*n* = 408)	*p* value
Asymptomatic	3 (11.5)	74 (18.1)	0.596
Nasal obstruction	7 (26.9)	118 (28.9)	0.827
Post nasal drip	13 (50)	111 (27.2)	0.013*
Mucopurulent rhinorrhea	12 (46.2)	95 (23.3)	0.009*
Foul odor	6 (23.1)	38 (9.3)	0.037*
Olfactory disorder	2 (7.7)	10 (2.5)	0.157
Cough	1 (3.8)	21 (5.1)	1
Sputum	3 (11.5)	33 (8.1)	0.466
Headache	4 (15.4)	66 (16.2)	1
Toothache	1 (3.8)	16 (3.9)	1
Orbital pain	2 (7.7)	12 (2.9)	0.202
Facial pain	1 (3.8)	50 (12.3)	0.342

BFB Bilateral fungal ball, *UFB* unilateral fungal ball

*$p < 0.05$

symptoms. These patients had undergone CT or MRI as part of a health examination or diagnosis of other diseases, and FB was diagnosed via a postoperative pathological examination. Nasal obstruction was found in 26.9% of patients in the BFB group and 28.9% in the UFB group ($p = 0.827$). More patients complained of facial pain in the UFB group (12.3%) than in the BFB group (3.8%), but without statistical significance ($p = 0.342$). In addition, there were no differences between the two groups in regards to complaints of headache, toothache, and orbital pain. However, postnasal drip (50% vs. 27.2%, $p = 0.013$), mucopurulent rhinorrhea (46.2% vs. 23.3%, $p = 0.009$), and foul odor (23.1% vs. 9.3%, $p = 0.037$) were more frequent in the BFB group than in the UFB group, with statistical significance.

Comparison of CT findings

The CT features of the two groups are shown in Table 3. Septal deviation was observed in 46.2% of patients in the BFB group and 38.6% in the UFB group ($p = 0.442$). Concha bullosa was found in 19.2% in the BFB group and 7.6% in the UFB group ($p = 0.054$). The proportion of Haller cells was similar between the BFB and UFB groups (15.4% and 15.2%, respectively, $p = 1.000$). Calcification was observed in 80.8% in the BFB group and 73% in the UFB group ($p = 0.383$). In contrast, soft-tissue density was noted in 19.2% in the BFB group and 26.2% in the UFB group ($p = 0.429$). In both groups, calcification was more frequent than soft-tissue density. A comparison of the involved sinuses showed no statistically significant intergroup differences in the maxillary, ethmoid, and frontal sinuses. Meanwhile, sphenoid sinus involvement was observed in 30.8% in the BFB group and in 11.8% in the UFB group, with a statistically significant difference ($p = 0.011$).

We also evaluated the location of involved sinuses in patients with BFB (Table 4). In 21 (80.8%) patients, one sinus on each side was involved, whereas, in five (19.2%) patients, one or more sinuses were involved on each side. The most commonly involved sinus in BFB was the maxillary sinus on each side in 15 (57.7%) patients. In cases of

Table 3 Analysis of computed tomography findings

	BFB (*n* = 26)	UFB (*n* = 408)	*p* value
Anatomical variation			
Septal deviation	12 (46.2)	157 (38.6)	0.442
Concha bullosa	5 (19.2)	31 (7.6)	0.054
Haller cell	4 (15.4)	62 (15.2)	1
Involved sinus			
Ethmoid sinus	4 (15.4)	88 (21.6)	0.454
Maxillary sinus	23 (88.5)	373 (91.4)	0.488
Frontal sinus	0 (0)	23 (5.6)	0.384
Sphenoid sinus	8 (30.8)	48 (11.8)	0.011*
Radiological appearance			
Calcification	21 (80.8)	297 (73)	0.383
Soft tissue density	5 (19.2)	107 (26.2)	0.429

BFB bilateral fungal ball, *UFB* unilateral fungal ball

*$p < 0.05$

Table 4 Locational characteristics of bilateral fungal ball

Location (one side–the other side)	*n* (%)
1 sinus on each side	21 (80.8)
M–M	15 (57.7)
M–E	2 (7.7)
M–S	2 (7.7)
S–S	2 (7.7)
>1 sinus on each side	5 (19.2)
M–M+S	2 (7.7)
M–M+E	1 (3.8)
E–E+S	1 (3.8)
S–S+M	1 (3.8)

M maxillary sinus, *E* ethmoid sinus, *S* sphenoid sinus

Table 5 Treatment and outcomes

	BFB (*n* = 26)	UFB (*n* = 408)	*p* value
Treatment and outcome			
Endoscopic sinus surgery, *n* (%)	26 (100)	408 (100)	1
Follow-up periods, month ± SD	6.5 ± 5.4	6.6 ± 9.1	0.577
Recurrence, *n* (%)	2 (7.7)	10 (2.5)	0.157
Histopathology			
Aspergillus species, *n* (%)	24 (92.3)	385 (94.4)	0.655
Mucor species, *n* (%)	0	5 (1.2)	1
Candida species *n* (%)	0	4 (1.0)	1
Undetermined, *n* (%)	2 (7.7)	14 (3.4)	0.248

BFB Bilateral fungal ball, *UFB* unilateral fungal ball, *SD* standard deviation

more than one sinus on each side, bilateral maxillary sinus involvement was the most common; bilateral frontal sinus involvement was not observed.

Treatment and outcomes

A comparison of the treatment outcomes between the two groups is shown in Table 5. All patients in both the groups underwent endoscopic sinus surgery. The mean follow-up periods were 6.5 ± 5.4 months in the BFB group and 6.6 ± 9.1 months in the UFB group (*p* = 0.577). Two (7.7%) patients in the BFB group and 10 (2.5%) in the UFB group experienced recurrence, although without any statistical difference (*p* = 0.157). *Aspergillus* species was most commonly found in both groups (92.3% vs. 94.4%, respectively, *p* = 0.655). *Mucor* species (1.2%) and *Candida* species (1.0%) were observed only in the UFB group, although the difference was statistically insignificant. Two (7.7%) patients in the BFB group and 17 (3.4%) in the UFB group

had histologically confirmed fungal ball, but the subtypes were undetermined.

Discussion

Most cases of fungal ball in the paranasal sinus are known to occur in individuals of older age, an average age of 64 years [2]. The average age of the 8 patients with BFB who participated in the study by Lee et al. was 59.3 years [9]. In this study, all patients with UFB and BFB showed a similar age range (60–63 years). In addition, we found a two times higher female predominance for the incidence of both BFB and UFB unlike the 1:1 sex ratio of BFB in Lee et al. study [9]. These differences are believed to have resulted from the small number of BFB patients in the study by Lee et al. Nevertheless, our finding is consistent with that of other studies with respect to a female predominance [25–27]. There are several studies on the presence or absence of underlying diseases, such as hypertension and diabetes mellitus, in patients with FB [2, 19]. In previous reports, 8–14.6% of patients with FB had diabetes mellitus, which was similar to the results in the current study [19, 28]. In addition, other studies reported that 15–21.7% of patients with FB had hypertension [19, 28], although 61.5% of patients with BFB and 39% of those with UFB had hypertension in our study. Lee et al. [9] reported that two of eight patients with BFB had hypertension (25%). On the other hand, two diagnosed with BFB among the 69 FRS patients showed that all had hypertension (100%) [17]. Although the cause of the close relationship between hypertension and FB in this study is not clear, further studies are required to verify this relationship.

In the present study, an immunologic examination did not reveal an intergroup difference in total IgE levels. However, specific IgE positivity to *Dermatophagoides pteronyssinus*, *Clodosporium*, and *Aspergillus* was significantly higher in the BFB group. Although Collins et al. reported that AFRS was correlated with fungus-specific IgE levels [29], there has been no report of correlation between specific IgE and occurrence of FB to this day. We think that high specific IgE levels in BFB may be associated with easy FB formation after secondary obstruction due to an allergic reaction in the sinus. In addition, the racial and regional difference in allergic reaction may be related to these reactions. Nevertheless, further study will be required to understand the reason for the increased specific IgE positivity in BFB.

Lai et al. [22] described the common symptoms of FB, including nasal obstruction, mucopurulent discharge, postnasal drip, and facial pain, which are similar to those of chronic rhinosinusitis [13]. In this study, the main symptoms in the BFB group were postnasal drip, mucopurulent rhinorrhea, nasal obstruction, foul odor, and headache, in that order. Among these symptoms, postnasal drip, mucopurulent

rhinorrhea, and foul odor showed higher incidence in the BFB compared to UFB. Meanwhile, anatomical variations on CT, such as septal deviation, concha bullosa, and Haller cells, were not found to be correlated with the occurrence of FB [30]. Similarly, these anatomical variations did not significantly differ according to the occurrence of FB in this study. Maxillary sinus was the most commonly involved site of FB, similar to other reports [9, 22]. Also, sphenoid sinus in patients with BFB was more involved than in those with UFB. In addition, the percentages of calcification within the involved sinus on CT images were 80.8% in BFB and 73% in UFB, similar or somewhat higher to previous studies ranged from 66 to 69% [7, 9].

In other studies, endoscopic sinus surgery was performed for the treatment of FB, and the results were mostly successful [9, 13, 22, 28]. All patients in our study were also eligible for endoscopic surgery. Although recurrence rate was higher in BFB than in UFB, all cases of recurrence in BFB occurred in sphenoid sinus, and we assumed that it may be attributed to a poor surgical visual field and incomplete removal due to complicated anatomy. To prevent recurrence, surgeons must thoroughly examine the remaining lesion, especially parts that cannot be clearly visualized. In addition, postoperative pathological examination is needed to identify invasive or non-invasive FRS and to make a final diagnosis [3]. *Aspergillus* spp. are the most commonly found fungi in the FB [25]. In this study, fungal species were identified morphologically from a postoperative specimen, and more than 90% of BFB patients had *Aspergillus* species, which was similar to UFB patients and was in accordance with a previous report [25].

The merit of this paper is that it included more patients with BFB than did previous studies, thereby allowing for better representation of the clinical characteristics of BFB in Korea; BFB patients were more likely to have hypertension, more common nasal symptoms, and higher allergy positivity to fungi and kinds of house dust mite than UFB patients. However, the main drawback of this study is that the results can differ according to region and ethnicity. The clinical features in Western and other Asian countries may different. Thus, a comparison study according to region and ethnicity need be followed to verify our findings.

Conclusion

Although treatments and outcomes were similar between BFB and UFB in this study, patients with BFB in Korea showed more common hypertension and symptoms of foul odor, mucopurulent rhinorrhea, and postnasal drip with allergy positivity than those with UFB. Therefore, understanding clinical characteristics of BFB will help clinicians to approach BFB more appropriately.

Compliance with ethical standards

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