Analysis of predisposing factors in unilateral maxillary sinus fungal ball: the predictive role of odontogenic and anatomical factors*

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Abstract

Background: The pathogenesis of maxillary sinus fungal ball (MSFB) is explained by aerogenic and odontogenic factors. We evaluated the predisposing factors, including intranasal anatomical and dental factors for increased diagnostic accuracy.

Methodology: In this study, 117 patients who underwent endoscopic sinus surgery for unilateral MSFB were included. Preoperative computed tomography (CT) scans were used to analyze the presence of anatomical variations (anterior and posterior nasal septal deviation (NSD), concha bullosa (CB), infraorbital cell (haller cell), paradoxical middle turbinate, everted uncinate process and MS size). Dental factors including history of dental procedures and findings on CT scans were reviewed.

Results: Anterior and posterior NSD toward non-affected side were significantly associated with the presence of FB. The presence of CB and infraorbital cell was higher in the non-affected side rather than in the lesion side. Compared to non-affected MS, FB-presence MS was shallower and had a larger height to depth ratio. The presence of dental history was significantly higher on FB-presence MS than non-affected MS. In multivariable analysis, posterior NSD toward non-affected side, dental history increased the aOR of MSFB, while the presence of CB and infraorbital cell decreased the aOR of MSFB.

Conclusions: The occurrence of MSFB seems to be associated with ipsilateral odontogenic factors, followed by anatomic variations including posterior NSD toward non-affected side and absence of CB and infraorbital cell.

Key words: fungal ball, maxillary sinus, odontogenic, septal deviation, volume

Introduction

Sinonasal fungal balls (FBs) are the most common type of noninvasive fungal rhinosinusitis and its prevalence has dramatically increased over the past 10 years (1). They occur most frequently in elderly women, and Aspergillus sp. is the main causative organism (2). Endoscopic sinus surgery (ESS) is the treatment of choice, and antifungal agents are not required after ESS (3). FB mainly occurs unilaterally rather than bilaterally and occurs most often in the maxillary sinus (MS), followed by the sphenoid sinus (4).

Although the pathogenesis of MSFBs is still controversial, it has been largely explained by local factors, including aerogenic and/or odontogenic factors (5). Regarding aerogenic factors, previous studies have investigated the role of certain sinonasal anatomical variations on FB formation, suggesting that an altered nasal drainage pathway due to anatomical variation might facilitate trapping of fungal spores and/or provide the anaerobic conditions for MS (6-8). Additionally, FB formation is also thought to be associated with the inflammatory process related to the odontogenic factors of the maxillary teeth (9,10). Case-control studies (e.g., patients with FB vs. control subjects and/or chronic rhinosinusitis) have been commonly performed to identify the effect of several local factors on FB pathogenesis (5,9). In these studies, various predisposing factors such as nasal septal deviation (NSD), presence of concha bullosa (CB), the shape of the uncinate process, and history of endodontic treatment have been analyzed individually to determine whether they could be independent risk factors for FB formation [6,7,9,10]. However, the etiology of FB formation remains unclear, and there is still some debate. Moreover, most studies compared diseased subjects with control subjects, despite patients having unilateral lesions. Therefore, we evaluate predisposing factors for FB formation by comparing the diseased side with the disease-free side of the nasal cavity and paranasal sinus. Additionally, we also sought to identify if there are any clinical predisposing factors of MSFB increasing the preoperative prediction of the MSFB.

Materials and methods

We reviewed the electronic medical records (EMRs) and preoperative computed tomography (CT) scans of patients with unilateral MSFB who were diagnosed with pathological confirmation by using special stains such as Haematoxylin and Eosin, Periodic Acid Schiff, and Gomori Methamine Silver stains of FB after ESS at the Kyung Hee Medical Center between January 2000 and April 2021. The Institutional Review Boards of our institute approved this study (IRB No. KHU 2021-12-001). Patients with bilateral or multiple FB in the paranasal sinuses were excluded. We identified 117 patients with unilateral MSFB and reviewed their demographics. The patients' history of dental procedures (e.g., implantations, root canal treatments, and extractions) on the side of the MSFB and contralateral side were analyzed. Additionally, positive findings on CT scan were defined as oroantral fistula on the maxilla, protrusion of the dental root, and implantation of maxillary teeth.

Regarding anatomical factors, we hypothesized that anatomical variations affecting nasal airflow, ostiomeatal unit (OMU) narrowing, and MS size could be associated with unilateral MSFB formation. First, NSD was analyzed by dividing it into anterior deviation and posterior deviation. The anterior deviation was defined as the level at the anterior end of the inferior turbinate, and posterior deviation was defined as the level of the OMU on the coronal view (Figure 1) [7]. Second, the presence of infraorbital cell, paradoxical middle turbinate, everted uncinate process, CB, and well-aerated frontal sinus with patent frontal recess was analyzed to determine the anatomical factors affecting the OMU. Lastly, the height (mm), width (mm), and depth (mm) of both sides of the MS were measured by preoperative CT in all patients. The height was measured in the coronal view and was defined as the longest distance from the highest point of the sinus roof to the lowest point of the sinus floor (Figure 2A). The width and depth were measured from the axial view. Width was defined as the longest distance perpendicular from the lateral process of the MS to the medial wall of the sinus (Figure 2B). Depth was defined as the longest distance from the most anterior point to the most posterior point of the medial wall (Figure 2C) [11]. Two otorhinolaryngologists who were blinded to the patients' information performed all measurements. Using these three lengths, the shape and volume of each MS were calculated and analyzed using the height-to-width and the height-to-depth ratios.

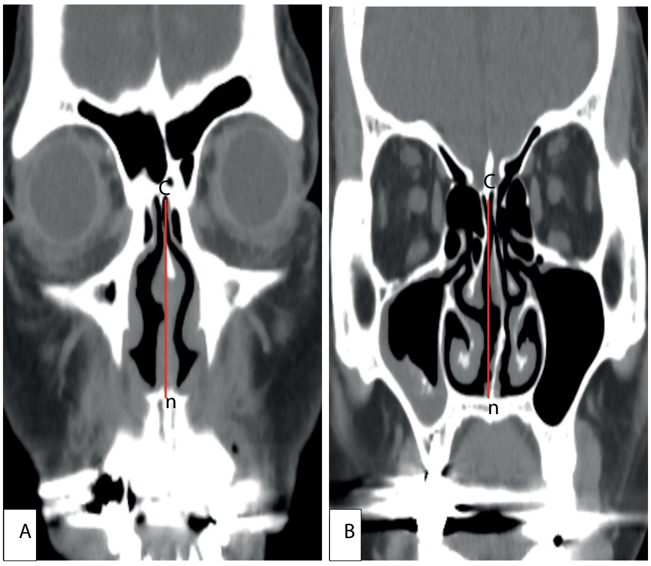

Figure 1. Left-sided deviation of the nasal septum at the nasal valve level (A) and the ostiomeatal unit level (B). point c, crista galli; point n, anterior nasal spine.

Figure 2. Measurement of the maxillary sinus. A. Height of the maxillary sinus on coronal view; B. Width of the maxillary sinus on axial view; C. Depth of the maxillary sinus on axial view.

Table 1a. Volumetric measurements of maxillary sinus.

Variable	FB-presence MS (mean ± SD)	Non-affected MS (mean ± SD)	p-value
Height (mm)	40.19±5.46	40.41±5.87	0.48
Width (mm)	28.58±5.00	27.58±4.84	0.03*
Depth (mm)	36.58±4.10	38.39±3.91	<0.001**
Volume (mm³)	21598.90±7312.24	22316.30±7762.46	0.07
H/W ratio	1.43±0.22	1.47±0.21	0.03*
H/D ratio	1.11±0.15	0.05±0.13	<0.001**

Abbreviations: FB, fungal ball; MS, maxillary sinus; SD, standard deviation; H/W, height to width; H/D, height to depth. *Significant at p<0.05 **significant at p<0.001.

Table 1b. Volumetric measurements of maxillary sinus (except medial expansion).

Variable	FB-presence MS (mean ± SD)	Non-affected MS (mean ± SD)	p-value
Height (mm)	39.12±5.49	38.98±5.61	0.749
Width (mm)	27.02±4.79	26.81±4.60	0.607
Depth (mm)	36.79±4.23	37.75±3.59	0.018*
Volume (mm³)	19985.62±6758.12	20310.72±6758.79	0.517
H/W ratio	1.47±0.22	1.47±0.22	0.913
H/D ratio	1.07±0.16	1.04±0.14	0.037*

Abbreviations: FB, fungal ball; MS, maxillary sinus; SD, standard deviation; H/W, height to width; H/D, height to depth. *Significant at p<0.05 **significant at p<0.001.

Subsequently, the volume of each MS was calculated using the following equation [12].

MS volume (mm^3) = (height x depth x width) x 0.5

Statistical analysis

Statistical analyses were performed using SPSS ver. 20 (SPSS Inc., Chicago, IL, USA). The paired t-test was used to compare the volume and shape of the MS with and without FB. The chi-square test was used to investigate etiological correlations between the presence or absence of FB in each MS, as well as the anatomical and odontogenic factors described above. Multivariable logistic regression analysis was performed to evaluate the role of these etiological factors in the occurrence of unilateral MSFB. The same variables analyzed in the univariable analysis were entered into a stepwise logistic regression analysis. Additionally, we measured the diagnostic value of the predisposing factors for MSFB by accessing the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A p-value < 0.05 was considered significant.

Results

The mean age of the 117 patients was 63.7 years (range, 22–88 years), of which 45 were male and 72 were female. Of the 117 patients, eight were diagnosed with allergic rhinitis and four were diagnosed with asthma. In this study, there were 90 cases of aspergillosis, 1 case of mucormycosis, and 26 cases of unspecified fungal disease based on histopathologic examination. Among the 90 cases of aspergillosis, four cases accompanied actinomycosis. The mean follow-up period was 11.23 months (range 0.5 to 120 months) after ESS, and there was no recurrence or revision surgery.

Table 1a, and 1b summarizes the results of the mean height, mean width, mean depth, volume, and the ratio of both MSs. There was no significant difference in the volume between the MS with and without FB (all p>0.05). Interestingly, there was a statistically significant difference in the shape of each MS. The FB-presence MS was wider (mean width= 28.58mm vs 27.58mm, p=0.03) and shallower (mean depth= 36.58mm vs 38.39mm, p<0.001) than the non-affected MS. The FB-presence MS had a larger height to depth ratio (p<0.001) and a smaller height to width ratio (p=0.03) than the non-affected MS (Table 1a). Since the medial expansion of the fungal ball likely acts as a bias, we excluded cases that fungal ball medial expansion leads to uncinate process banding. Table 1b summarizes the further analysis of the volume and shape of the bilateral maxillary sinuses in remaining 50 patients. The FB-presence MS was shallower (mean depth= 36.79mm vs 37.75mm, p=0.018) and had a larger height to depth ratio (p=0.037) than non-affected Ms. However, there was no significant difference in the width of maxillary sinus, and the height to width ratio between the MS with and without FB

Table 2. Predisposing factors associated with unilateral MSFB.

Variable	FB-presence MS n (%)	Non-affected MS n (%)	p-value
Anatomical factors			
Anterior NSD toward non-affected side	68 (58.1)	49 (41.9)	0.01*
Posterior NSD toward non-affected side	71 (60.7)	46 (39.3)	0.001*
Concha bullosa	27 (23.1)	42 (35.9)	0.03*
Infraorbital cell	7 (6.0)	15 (12.8)	0.07
Frontal cell	108 (92.3)	112 (95.7)	0.27
Paradoxical MT	7 (6.0)	3 (5.0)	0.20
Everted UP	14 (12.0)	15 (12.8)	0.84
Odontogenic factors			
Dental history	15 (12.8)	1 (0.9)	<0.001**
CT findings	22 (18.8)	20 (17.1)	0.73

Abbreviations: MSFB, maxillary sinus fungal ball; FB, fungal ball; MS, maxillary sinus; NSD, nasal septal deviation; MT, middle turbinate; UP, uncinate process; CT, computed tomography. *Significant at p<0.05 **significant at p<0.001.

Table 3. Associations of the predisposing factors and unilateral MSFB.

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p-value	Adjusted Odds ratio (95% CI)	p-value
Anatomical factor				
Anterior NSD toward non-affected side	1.93 (1.15-3.24)	0.01*	NA	
Posterior NSD toward non-affected side	2.38 (1.41-4.03)	0.001*	2.46 (1.41-4.29)	0.001*
Concha bullosa	0.54 (0.30-0.95)	0.03*	0.50 (0.27-0.93)	0.03*
Infraorbital cell	0.43 (0.17-1.10)	0.07	0.33 (0.12-0.93)	0.04*
Fontal cell	0.54 (0.17-1.65)	0.27	NA	
Paradoxical MT	2.42 (0.61-9.59)	0.20	NA	
Everted UP	0.92 (0.42-2.01)	0.84	NA	
Odontogenic factor				
Dental history	17.06 (2.21-131.41)	<0.001**	20.70 (2.55-168.28)	0.01*
CT findings	1.12 (0.58-2.19)	0.73	NA	

Abbreviations: MSFB, maxillary sinus fungal ball; CI, confidence interval; NSD, nasal septal deviation; MT, middle turbinate; UP, uncinate process; CT, computed tomography. *Significant at p<0.05 **significant at p<0.001.

(p>0.05).

The presence of the variables thought to affect the occurrence of unilateral MSFB is summarized in Table 2. Anterior NSD toward non-affected side (58.1% vs 41.9%), posterior NSD toward non-affected side (60.7% vs 39.3%), CB (23.1% vs 35.9%), and history of dental procedures (12.8% vs 0.9%) showed statistically significant differences in frequency between FB-presence MS and non-affected MS.

The univariable analysis results that were used to investigate the predisposing factors that selectively form an FB only in one of the bilateral MS are the following (Table 3): NSD was significantly associated with unilateral MSFB; anterior NSD toward non-affected side had a statistically significant increased odds ratio (OR) of unilateral MSFB (OR=1.93, 95% confidence interval (CI), 1.15-3.24, p=0.01); and posterior NSD toward non-affected side also showed an increased odds ratio of unilateral MSFB (OR=2.38, 95% CI, 1.41-4.03, p=0.001). The presence of CB decreased the odds ratio of unilateral MSFB (OR=0.54, 95% CI, 0.30-0.95, p=0.03). A similar trend was found in the presence of infraorbital cell; however, the difference was not statistically significant. On the other hand, other anatomical factors, including the presence of frontal cells, paradoxical middle turbinate, and everted uncinate process, were not statistically significant. A previous history of ipsilateral dental procedures showed a significantly higher odds ratio for unilateral MSFB (OR=17.06, 95% CI, 2.21-131.41, p<0.001).

As shown in Table 3, multivariable analysis revealed that anatomical factors showed adjusted odds ratios (aOR) for unilateral MSFB. A history of ipsilateral dental procedures showed the highest odds ratio of unilateral MSFB (aOR=20.70, 95% CI, 2.55-168.28, p=0.01). In the case of posterior NSD toward non-affected side, the odds ratio of unilateral MSFB was increased (aOR=2.46, 95% CI, 1.41-4.29, p=0.001); however, the presence of CB (aOR=0.50, 95% CI, 0.27-0.93, p=0.03) and infraorbital cell (aOR=0.33, 95% CI, 0.12-0.93, p=0.04) decreased the odds ratio of unilateral MSFB.

Lastly, in our analysis, the sensitivities of the absence of CB and infraorbital cell were 76.9% (35.8% specificity, 54.5% PPV, and 60.9% NPV) and 94% (12.8% specificity, 51.9% PPV, and 68.0% NPV), respectively. Regarding a history of ipsilateral dental procedures, specificity was 89.7%, while sensitivity was 25.6% (71.4% PPV, 54.7% NPV). Additionally, the presence of posterior NSD toward non-affected side showed similar degree of sensitivity and specificity (both, 60.6%).

Discussion

The prevalence of FB has increased over the past 10 years [13,14] and is commonly encountered in older women [1]. The efforts to identify possible pathophysiological mechanisms and predisposing factors underlying the development of MSFB is important for the treatment of MSFB. Moreover, the FB may have a possibility of the progression to the invasive form in patients with immunocompromised status, suggesting that early diagnosis is regarded as fundamentally important. Additionally, based on the previous reports [15,16], we think that early diagnosis is also relevant and advisable for some immunocompetent patients (e.g., elderly patients, diabetes under treatment, patients experienced chronic renal disease) to minimize the risk of developing invasive fungal rhinosinusitis. In this study, we sought to analyze the predisposing factors that could contribute to unilateral MSFB formation, including aerogenic, odontogenic, and mixed pathways. Notably, we found that among the numerous predisposing factors, a previous history of dental procedure was the most significant factor related to unilateral MSFB, followed by factors contributing to the concavity of the nasal cavity (Table 3). To our knowledge, this is the first study to thoroughly analyze the effects of possible risk factors for unilateral MSFB formation by using multivariable analysis in the case-control design with the contralateral healthy side as control. Moreover, we sought to demonstrate the sensitivities and specificities of these risk factors to clarify the clinical implication.

To date, there are only a few reports evaluating the relationship between the volume of MS and the presence of unilateral MSFB [17]. Michel et al. reported that there was a significant statistical difference in volume between diseased MS and disease-free MS in the FB group [17]. In addition, a FB was found in the smallest MS of the FB group (93%). They suggested that MSFB was associated with a smaller size of MS [17]. In our study, the volumes of both MSs were not statistically different (p>0.05). The above study used the 3D reconstruction method to measure the volume of the MS. We manually measured the three-dimensional length of MS and calculated the volume of MS using formula. Sahlstrand-Johnson et al. reported good concordance between the manually and automatically calculated volume of MS (18). Bhandarkar et al. reported that persistent inflammation of mucosa led to reduced viability of the underlying bone, resulting in development of bony thickening and neo-genesis (19). This mechanism might contribute to the inner volume of the diseased MS. Therefore, it is unlikely that the smaller volume of the affected MS is a result of unilateral MSFB or a predisposing factor of unilateral MSFB. To date, no study has analyzed the shape of bilateral MSs. In our study, compared to non-affected MS, the mean width and mean depth of FB-presence MS were 1 mm longer (p=0.03) and 1.8 mm shorter (p<0.001), respectively (Table 1a). As a result of further analysis, FB-presence MS was 1 mm shorter than non-affected MS at mean depth (p=0.018) (Table 1b). There was no difference in the mean height of either MS group. Taken together in Table 1a and 1b, the reason FB-presence MS was wider than non-affected MS was probably an expansion of maxillary sinus medial wall by fungal ball. The FB-presence MS group showed shallower MSs than the non-affected MS group. Further studies are needed to identify the potential mechanisms underlying the observed effect of MS shape on FB formation.

The relationship between FB formation in unilateral MS and anatomical factors, including NSD and variants affecting OMU patency, is still unclear. Yoon et al. reported that there was no association between the presence of NSD, CB, and infraorbital cell and the location of the MSFB [13]. Tsai et al. also reported that there was no statistical significance between NSD, CB, and sinus FB [20]. Another study reported that NSD and infraorbital cell were not associated with the location of MSFB, while CB tended to be observed more frequently in the contralateral side of MS (p=0.099). When men and women were analyzed separately, in only male patients, the concave side due to the NSD was statistically significant with the location of MSFB (p=0.006) [21]. Contrary to the above studies, we analyzed NSD by dividing it into anterior deviation and posterior deviation according to Hwang [7]. The univariable analysis showed that the anterior and posterior NSD toward non-affected side were associated with unilateral MSFB. In particular, the effect of posterior NSD toward non-affected side on unilateral MSFB was also significant in the multivariable analysis. Regarding another anatomical factors, we found that infraorbital cells tended to be associated with the location of FB in univariable analysis (p=0.07). Moreover, multivariable analysis showed that the presence of infraorbital cell

as well as CB reduced the formation of ipsilateral MSFB. In our analysis, the sensitivities of the absence of CB and infraorbital cell were 76.9% and 94%, suggesting that the absence of CB and infraorbital cell may be an important clue to ipsilateral MSFB.
Computational fluid dynamics (CFD) has been widely used to investigate the aerodynamics in the nasal cavity, and has shown that it is possible to predict the air velocity, airflow temperature, nasal resistance, pressure, flow partitioning, wall sheer stress, and turbulence kinetic energy in the nasal cavity [22,23]. According to Li, in the concave side of the OMU area, airflow minimal temperature and airflow velocity were lower and the turbulence kinetic energy was higher than that in the convex side [22]. Sinus hypoventilation and anaerobic condition lead to low pH, which would promote initial fungal growth [24]. However, OMU obstruction did not support MSFB [8]. Combining the above results with our findings, one possible hypothesis is that a relatively larger nasal cavity due to posterior NSD toward non-affected side and an absence of CB and/or infraorbital cell around the OMU compared to the opposite side facilitate airborne fungal spores entering through the ostium of MS, resulting in the development of unilateral MSFB. Moreover, altered mucociliary clearance, especially in elderly subjects, might also contribute to entrapping fungal spores in MS. Further investigation is needed to confirm this hypothesis.
Odontogenic factors have also been considered as possible risk factors for MSFB formation [9,10]. It is generally believed that initial fungal colonization can occur through oroantral communication [10]. Additionally, the inflammation associated with dental procedures on maxillary teeth and filling materials extruded in MS may be involved in the development of MSFB (25). We also found that a history of dental procedures was the most significant predisposing factor for the occurrence of unilateral MSFB, as demonstrated by univariable (OR 17.06, 95% CI, 2.21-131.41) and multivariable analysis (aOR 20.70, 95% CI, 2.55-168.28) (Table 3). Additionally, we found relatively high specificity (89.7%) of personal dental history for unilateral FSFB. Altogether, the history of dental procedures plays a greater role in the occurrence of unilateral MSFB than the aerogenic pathway. In this study, univariable and multivariable analysis results were inconsistent between dental history and positive findings on CT scans. When data were collected, dental history and positive findings on CT scans were defined as 1) positive findings on CT scans includes oroantral fistula on the maxillar, protrusion of the dental root, and implantation of maxillary teeth, and 2) past dental history includes implantations, root canal treatments, and extractions. Basurrah et al. suggested that manipulation of the maxillary sinus mucosa during endodontic treatment (tooth extraction and dental procedures) was related to fungal maxillary sinusitis [26]. According to this study, implantations, root canal treatments, and extractions were factors that affect the sinus mucosa in maxillary sinus fungal ball formation. Root canal treatments and extractions were not defined as findings on CT scans, so it is thought to show inconsistent results.
It has been reported that 50% to 83% of intralesional hyperdensity lesions including calcification are observed on preoperative CT in FB patients [27]. It is difficult to differentiate unilateral chronic rhinosinusitis (CRS) from unilateral FB when CT findings are ambiguous. Because the first-line treatment for CRS (medical therapy) and FB (surgical removal) is different, these two diseases should be differentiated. Given our findings, we suggest that if there is a history of dental procedures on the disease-present side, or in the presence of anatomical variations near the OMU in patients with unilateral chronic rhinosinusitis, the possibility of unilateral MSFB should be considered even in the absence of characteristic findings of fungal sinusitis on CT (e.g., calcification, and intralesional hyperdensity). In these cases, we suggest that early suspicion of FB and surgical treatment is necessary than long-term antibiotic treatment.
Despite possible risk factors for unilateral MSFB formation were thoroughly analyze, this study has several limitations. First, this is a single center study with retrospective design and a relatively small number of subjects are included. Second, we measure MS volume by using the equation and physiological role of the sinus volume is not identified in this study. Third, although numerous variations of NSD exist, we only used the anterior and posterior categories in our study. Furthermore, since it has been shown that the variability of the deviation angle did not affect the aerodynamic disturbance around the OMU, the severity of the deviated angle was not taken into account [22].

Conclusions

We found that unilateral MSFB was significantly associated with ipsilateral odontogenic factors and anatomic variations near the OMU, including posterior NSD toward non-affected side and the absence of CB and infraorbital cell.

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Authorship contribution

JGD: concept and design, writing, statistical analysis; HKM: statistical analysis, Data collection; GWC: Data collection, statistical analysis; SWK: concept and design, interpretation of data; JYM: concept and desing, interpretation of data, supervision.

Conflict of interest

None.

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