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Fungal Sinusitis: A Ten-Year Experience at King Abdulaziz University Hospital

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Abstract. Fungal sinusitis is frequently encountered in daily clinical practice. The aim of this study is to determine the most common causative pathogen and effectiveness of different methods for diagnosis fungal sinusitis. A retrospective study was performed on patients with different types of fungal sinusitis who had undergone endoscopic sinus surgery at King Abdulaziz University Hospital, Jeddah, from January 2001 to January 2011. 34 patients were then proven to have fungal sinusitis based on fungal culture. 11 patients were male (32.4%) and 23 patients were female (67.6%). *Aspergillus* species was the only causative agent identified. Radiology was the most sensitive test (100%). However, when histopathology, radiology and intra-operative examination were compared with results of fungal cultures, histopathology was the most specific test. Fungal sinusitis is not uncommon among patients followed up for chronic sinusitis at King Abdulaziz University Hospital. *Aspergillus* species is the main causative agent in these patients. Radiology is an excellent tool in providing a pre-operative diagnosis of this condition, and it should be followed by an extensive work-up, including histopathology and fungal cultures.

Keywords: Allergic fungal sinusitis, Allergic mucin, *Aspergillus*, Invasive fungal sinusitis.

Introduction

Fungal infection is a known cause of sinusitis, which is increasingly encountered in daily clinical practice. Fungal sinusitis is histologically

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classified into five distinct categories, namely allergic, noninvasive fungal colonization, chronic granulomatous, chronic invasive, and acute fulminant[1]. Most fungal infections of the sinuses are benign or non-invasive. Invasive forms are usually encountered in immunocompromised subjects, but some reports have described these forms in immunocompetent individuals[2-4].

It is important for the clinician to distinguish invasive from non-invasive disease as the prognosis and treatment are different for each. The invasive form, which is usually encountered in immunocompromised subjects, is characterized by its invasiveness, destruction of tissues, and rapid onset[5,6]. On the other hand, the non-invasive form of the disease has a longer course and is treated for extensive periods as chronic sinusitis before the condition is recognized[7]. Clinicians need a high index of suspicion in establishing the diagnosis as there are no clear-cut differences in the clinical presentation of both forms of the disease. Several diagnostic methods have proved useful in helping clinicians make an accurate diagnosis of fungal sinusitis. The use of imaging techniques such as paranasal sinus computed tomography (CT) are helpful in the pre-operative diagnosis of acute fungal sinusitis[8]. The extent of tissue involvement can be assessed intra-operatively and determined by histopathological examination[1,2,9,10]. The use of fungal dyes and in some cases, frozen sections, have been shown to be helpful in identifying fungal hyphae and the extent of tissue invasion[1,2]. Fungal cultures are necessary in identifying the causal agent, which in most studies reported in the literature involves two species: *Aspergillus* and *Mucor*[1,2,6,9-12].

The treatment options for fungal sinusitis are diverse and may involve the use of anti-allergic agents, antifungal drugs, corticosteroids and/or surgery. For most cases of fungal sinusitis, surgery is the treatment of choice[13]. The use of antibiotics is controversial but is usually prescribed post-operatively following debridement. The rate of relapse is high despite appropriate medical and surgical treatment[11,14]. More so, the follow up time is usually very lengthy, and it might involve the performance of endoscopic examinations and debridement on periodic bases, posing a financial burden on patients who already have a diminished quality of life[2,11,15]. Proper diagnosis and management will help in reducing the morbidity of this condition and improve patients' quality of life. Thus, the main objective of this study was to determine

the most common cause of fungal sinusitis in patients who consulted at King Abdulaziz University Hospital (KAUH) and to compare the result of histopathology, radiology and intra-operative examination with the results of fungal culture.

Materials and Methods

Retrospectively, we reviewed the records of 243 patients, who had undergone functional endoscopic sinus surgery (FESS) for chronic sinusitis at KAUH, Jeddah, from January 2001 to January 2011. The study included patients with allergic fungal sinusitis (AFS) based on the following criteria: (1) Presence of allergic mucin within the sinuses; (2) Detection of fungi by means of culture; (3) Absence of fungal invasion of the submucosa, blood vessels or bone; (4) Absence of diabetes or immunodeficiency state; and (5) Characteristic CT scan features. The inclusion criteria for cases with invasive fungal sinusitis (IFS) were signs suggestive of fungal sinusitis on radiology (CT and magnetic resonance imaging [MRI]) and presence of fungal hyphae in the submucosa, blood vessels, and bone. All cases of non-fungal sinusitis were excluded. The Biomedical Ethical Research Committee of the Faculty of Medicine, KAUH approved the study.

For all patients included in this study, the operative notes, radiology and histopathology reports as well as the culture findings were reviewed.

Collection and treatment of surgical specimens: Mucus was obtained with a suction apparatus, and the specimens were immediately placed in sterile normal saline bottles. Fungal sinusitis was suspected intra-operatively based on the presence of allergic mucin, described as an inspissated, tenacious, and highly viscous substance with a "peanut butter-like" like color[10]. Samples were taken to the histopathology and microbiology laboratories for microscopic examination and culture, respectively. Histologic examination of the samples was performed by staining with Gomori's Methenamine Silver (GMS) and Periodic Acid-Schiff (PAS) to identify fungal structures. Fungal cultures were done by standard methods on Sabouraud's agar media.

Management

The strategy involved a multimodality approach, including medical treatment and surgical debridement. All patients with AFS were

managed by FESS, while those with IFS had fungal treatment with amphotericin B (orally and locally by irrigation) and FESS.

Follow up

Patients were scheduled for regular follow-up every 3 months to identify possible recurrence. This included a clinical examination and the performance of paranasal sinus CT scans when indicated. Recurrence was based on reappearance of symptoms and radiological evidence of the disease on repeat scans. All cases of suspected recurrence were managed either medically or scheduled for repeat surgery depending on the presentation of the patient.

Statistical Analysis

Descriptive statistics was performed using the Statistical Package for the Social Sciences (SPSS for Windows, release 9.0; SPSS, Chicago, IL). Continuous variables were expressed as mean (SD) and frequency (percent). Fisher's exact test was used to compare the frequency of fungal and non-fungal infection among males and females. A p value < 0.05 was considered significant.

Results

Forty (16.5%) patients out of 243 cases, who had undergone FESS for chronic sinusitis, were included in the study; and diagnosed with fungal sinusitis based on Radiological diagnosis. 34 patients were then proven to have fungal sinusitis based on fungal culture. 11 patients were male (32.4%) and 23 patients were female (67.6%). 24 cases met the criteria for AFS, while 3 met the criteria for acute IFS and 7 met the criteria for chronic IFS. The mean (SD) age of the patients was 27.3 (12.9) years (range, 8-67 years). Table 1 shows the baseline characteristics of the patients.

Table 1. Baseline characteristics of the patients*.

Characteristic	Fungal	Non-fungal	p Value
Age (years)	27.3 (12.9)	37.3 (19.5)	0.112
Gender			
Male	11 [32.4%]	3 [50.0%]	0.650
Female	23 [67.6%]	3 [50.0%]	

**Data are presented as mean (SD) and as frequency [percent] unless otherwise indicated. The diagnosis of fungal sinusitis was based on the results of fungal cultures. The age range of the patients (n = 40) was 8-67 years with mean (SD) of 28.8 (14.3) years. The age range for patients who had positive results was 8-54 years.*

All the patients had a radiologic diagnosis of fungal sinusitis. Computed tomography of the paranasal sinuses showed hyperdense areas with hyperattenuation (Fig. 1) in all of the cases. In 10 of the cases, magnetic resonance imaging (MRI) showed heterogeneous low signal intensity in T1 and T2 weighted images and peripheral enhancement postcontrast administration, with extension into the cranium (Fig. 2) or orbit. Pansinusitis was documented in 18 cases; maxillary sinus involvement was noted in 32 cases (95%), followed by the ethmoid sinus in 30 patients (80%).

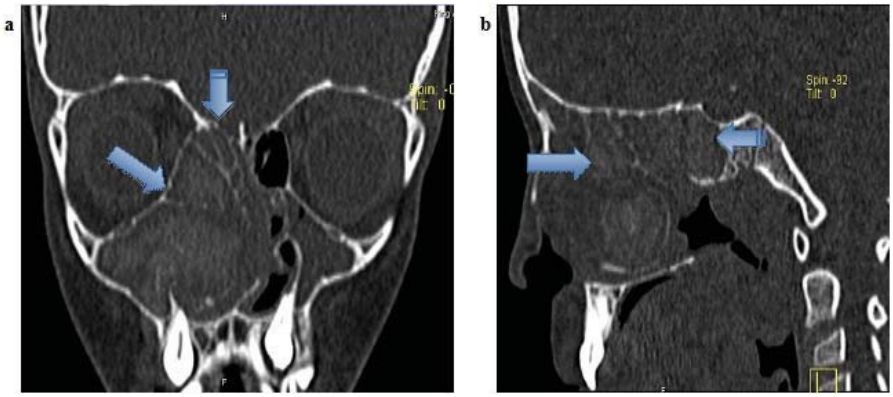

Fig. 1. Paranasal sinus CT scan of a patient with AFS: (a) There is marked opacification with hyperdense focus within the right maxillary sinus extending through the ostiomeatal complex. There is also destruction of the medial maxillary wall, demineralization and destruction of the lamina papyracea (arrow); however, the cribriform plate of the ethmoid appears intact (arrow). The nasal septum is seen to be deviated to the left. (b) The hyperdense focus also involves the anterior and posterior ethmoid sinuses (arrow), and extends to the right sphenoid sinus (arrow).

Mucin was observed intra-operatively in 92.5%. Histopathological examination of the allergic fungal sinusitis patients revealed branching non-invasive fungal hyphae, eosinophils and elongated eosinophilic bodies (Charcot-Leyden crystals) in 30% patients. And for patients with IFS, both acute and chronic, the histopathology revealed fungal hyphae invading the basement membrane. Fungi were isolated from the specimens of 34 patients (85%); 24 (60%) had AFS, while 10 (40%) had IFS; 7 were diagnosed as chronic IFS and 3 were acute IFS. *Aspergillus* was isolated from all 34 specimens. *A. flavus* was identified in 27 cases, *A. niger* in 3, *A. fumigatus* in 1, and the species was unidentified in 3 cases.

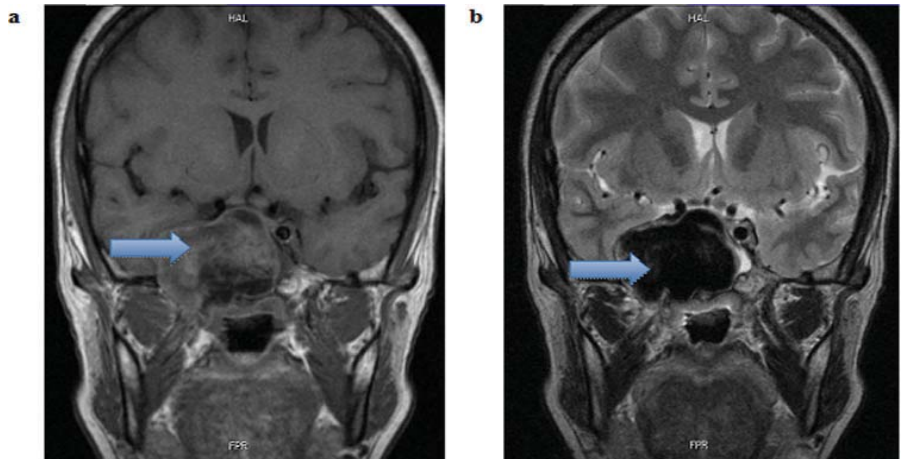

Fig. 2. **Magnetic resonance scans of a patient with IFS: (a) Coronal T1- and (b) T2-weighted images showing extensive involvement of sphenoidal air cells with high signal intensity on T1 (arrow) and an associated characteristic signal void on T2 (arrow) in keeping with fungal sinusitis. The sphenoidal component is extending to the cavernous sinus obstructing the right cavernous wall and extending intracranially to involve the right temporal lobe, the prepontine and suprasellar cisterns. It is compressing the left cavernous sinus with no definite invasion of the left side.**

Rereading the methods of diagnosis, histopathology had the highest rate of false negative result (60%), and the largest number of true positive results was observed with radiology (85%) followed by intra-operative diagnosis (82.5%). However, histopathology was more specific than radiology and intra-operative examination,

Moreover, radiological examinations provided the highest sensitivity for the diagnosis of fungal sinusitis, followed by intra-operative examinations, and lastly histopathology examinations (Table 2-3).

Table 2. **Number of positive and negative (true and false) results obtained with histopathology, radiology and intra-operative examination when compared with fungal culture results*.**

Examination	True Positive	False Positive	False Negative	True Negative
Histopathology	10 (25.0)	2 (5.0)	24 (60.0)	4 (10.0)
Radiology	34 (85.0)	4 (10.0)	0.0 (0.0)	2 (2.0)
Intra-operative	33 (82.5)	3 (7.5)	1 (2.5)	3 (7.5)

**Data are presented as frequency (percent).*

Table 3. Sensitivity and specificity of histopathology, radiology and intra-operative examination when compared with fungal culture results*.

Examination	Sensitivity	Specificity	PPV	NPV	Accuracy
Histopathology	29.41 (15.1-47.48)	66.67 (22.28-95.67)	83.33 (51.59-97.91)	14.29 (4.03-32.67)	35 (20.63-51.68)
Radiology	100.00 (89.72-100)	33.33 (4.33-77.72)	89.47 (75.2-97.06)	100.00 (15.81-100)	90 (76.34-97.21)
Intra-operative	97.06 (84.67-99.93)	50.00 (11.81-88.19)	91.67 (77.53-98.25)	75 (19.41-99.37)	90 (76.34-97.21)

**The data shown represent the sensitivity, specificity, PPV, NPV and accuracy with their corresponding 95% confidence intervals.*
Abbreviations: NPV = negative predictive value; PPV = positive predictive value.

Patients were followed up for a period of 4 years. The mean duration of follow-up was 24 months (range, 12-48 months). Among the 34 patients who had a diagnosis of fungal sinusitis on culture, relapse was noted in 20 patients, giving a relapse rate of 58.8%.

Discussion

Data from this study revealed that the frequency of fungal sinusitis among patients with chronic sinusitis at KAUH was 16.5%. Maxillary sinus involvement was documented in the majority of the cases (95%), and most patients had AFS (n = 28; 70%). Fungal cultures showed that *Aspergillus* species was the only causative agent isolated in the specimens of the patients. Radiology was the most sensitive test (100%) in the diagnosis of fungal sinusitis. However, when histopathology, radiology and intra-operative examination were compared with results of fungal cultures, histopathology was the most specific test (66.67%).

The criteria that was used for the diagnosis of patients with AFS in this study are similar to those defined by deShazo *et al.* in 1997[16]. Other classification criteria include the presence of nasal polyps and specific immunoglobulin titers[8,17]. Up to the early 2000s, there was no general consensus on the diagnosis of AFS, and according to a recent review, the probably most widely accepted criteria for the diagnosis of AFS makes use of major and minor criteria[18]. The major criteria are those proposed by Bent and Kuhn[17], which include: (1) Type I hypersensitivity (atopy) diagnosed by history, positive skin test, or serology; (2) The presence of nasal polyps; (3) Characteristic CT scan features; (4) Positive fungal smear; and (5) Presence of allergic mucin. There are six minor criteria, which are: (1) Asthma, (2) Unilateral

predominance, (3) Bone erosion on radiographs, (4) Positive fungal culture, (5) Presence of Charcot-Leyden crystals, and (6) Serum eosinophilia[18].

All our patients had a radiologic diagnosis of fungal sinusitis, and although radiological examination had a low specificity (33.3%) when compared with the results of fungal culture, we believe that it was critical in making a pre-operative diagnosis of fungal sinusitis because of its high sensitivity. Other authors found that the triad of nasal polyps, typical findings on CT and specific immunoglobulin E titers had a sensitivity of 70% and a specificity of 100% for the preoperative diagnosis of AFS[8]. Patients with AFS typically present hyperattenuating areas on CT scan as was the case in all our patients who had AFS[10,19]. Sinus expansion, remodeling and thinning of the bony sinus walls and bony erosion have also been described in patients with AFS[10,19,20]. Patients that have invasive form of the disease was considered based on earlier diagnostic criteria for IFS[21]. These criteria included the radiologic diagnosis of sinusitis and histopathological evidence of fungal structures within the sinus mucosa, submucosa, blood vessels or bone. In a recent review, the authors stated that in patients with AFS there should be no histopathological evidence for mucosal fungal invasion such as mucosal necrosis, granuloma formation, or giant cells[10]. While the issue of bone invasion in AFS seems confusing, many researchers have made suggestions to explain the mechanisms behind this. Some authors believe that the bone changes observed in AFS are probably due to pressure erosion caused by the expanding sinonasal mass as opposed to invasion by fungal hyphae[22]. Others suggested that inflammatory mediators are most likely the cause of bone erosion observed in these patients[20]. However, CT scans are unable to detect the bone changes caused by pressure erosion and direct fungal invasion. The radiologic features that have been documented in patients with IFS include the presence of hyperdense or moderately attenuating mass on unenhanced CT and on MRI, decreased signal intensity on T1 and much decreased signal intensity to signal void on T2[19,23].

Allergic mucin was identified intra-operatively in 92.5% of our patients. When compared with results of fungal cultures, the number of true positives was high 82.5%. This result prompts us to stress on the fact that when identified intra-operatively, all inspissated allergic mucin

should be evacuated as it has been shown that failure to do so is associated with higher relapse rates[24].

Fungal staining with GMS or PAS helps in identifying fungal hyphae within allergic mucin. Because identification of fungal genus/species after staining allergic mucin with fungal stains is often unreliable, fungal cultures are recommended[20]. In the literature, *Aspergillus* species is the most commonly identified organism in patients with fungal sinusitis [9,12,15,25]. In one study, *Aspergillus* was the only species found in 8 of the 11 cases diagnosed as AFS[5]. Al-Dousary isolated *Aspergillus* species in 67.8% of patients with AFS[25]. While Alrajhi reported a frequency of 32.0% among pediatric patients at King Faisal Specialist Hospital and Research Center, Riyadh[11]. Dematiaceous fungi have also been isolated in some patients with AFS; however, they are less frequent than *Aspergillus*[2,25]. Not identifiable was dematiaceous fungi in any of our samples.

The relapse rate in this study was 58.8%. However, it was determine individual rates amongst patients with AFS and amongst those with IFS as it was not an objective in this study. The high relapse rate in this study is not surprising as many authors have reported high rates of relapse in patients with AFS and in those with IFS[10,11,15,26]. Unfortunately, it is not possible to predict recurrence of the disease, and the factors that might be helpful in achieving long-term disease control in patients with fungal sinusitis are a comprehensive management plan involving medical and surgical care[27].

Conclusion

Fungal sinusitis is not an uncommon finding among patients followed up for chronic sinusitis at KAUH, and *Aspergillus* species is the main causative agent in these patients. Radiology is an excellent tool in providing a pre-operative diagnosis of this condition, and it should be followed by an extensive work-up, including histopathology and fungal cultures.

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التهاب الجيوب الأنفية الفطرية: خبرة عشر سنوات في مستشفى جامعة الملك عبد العزيز

خالد بريك الغامدي، والمؤيدبالله عبدالعزيز رمال، ورأفت صدقه سندي

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جدة – المملكة العربية السعودية

المستخلص. إن مرض التهاب الجيوب الأنفية الفطري التحسسي من الأمراض الأكثر شيوعا. وعليه فإن الهدف من هذه الدراسة هو دراسة مدى فاعلية طرق التشخيص المختلفة والمسبب الرئيسي لالتهاب الجيوب الأنفية الفطرية التحسسي في مرضى مستشفى جامعة الملك عبدالعزيز بجدة. أجرينا دراسة بأثر رجعي على المرضى الذين يعانون من التهاب الجيوب الأنفية الفطري التحسسي والتهاب الجيوب الأنفية الفطرية الغازية و الذين خضعوا لجراحة الجيوب الأنفية بالمنظار، من يناير ٢٠٠١ حتى يناير ٢٠١١. ثم مقارنة نتائج المزرعة الفطرية بنتائج الأشعة المقطعية و نتائج الفحص النسيجي للعينة.وكانت نتيجة البحث : نسبة مرضى التهاب الجيوب الأنفية الفطري بين مرضى التهاب الجيوب الأنفية المزمن هي ٥.١٦٪ (٤٠ حالة من ٢٤٣). واستوفوا ثمانية وعشرين مريضا معايير التشخيص لاتهاب الجيوب الأنفية الفطري التحسسي. فيما إستوفا اثنى عشر مريضا معاير التشخيص لإتهاب الجيوب الأنفية الفطرية الغازية. ونسبة الإناث ٦٥٪ من إجمالي مرضى الدراسة .التهاب الجيوب الأنفية الفطري هو مرض شائع

بين المرضى المصابين بالتهاب الجيوب الأنفية المزمن. والرشاشيات هي العامل الرئيسي المسبب للمرض في هؤلاء المرضى وأن الأشعة المقطعية هي أداة تشخيص ممتازة قبل العملية حيث وصلت نسبة حساسيتها للمرض إلى ١٠٠٪.