Medical Mycology February 2006, **44**, 61–67

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Paranasal sinus fungus ball: epidemiology, clinical features and diagnosis. A retrospective analysis of 173 cases from a single medical center in France, 1989–2002

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Over the last decade, we have observed a high frequency of *Aspergillus* rhinosinusitis in french medical centers. The epidemiological data, clinical presentations, radiology, mycology and histology results of 173 consecutive patients with paranasal sinus fungus balls who were admitted from 1989 to 2002 have been reviewed. The most common symptoms included purulent nasal discharges and nasal obstructions, with the maxillary sinus being the most common site of infection (152 cases, 87.8%). Computed tomography scans (CT scan) were performed in 92% (159/173) of the cases and heterogeneous opacities were observed in 132 patients (83%). Histology examinations were performed in all cases and proved positive in 162 patients. Fungi were recovered, mainly *Aspergillus fumigatus,* from samples of 50 patients, while specimens from the remaining 123 patients were negative. Since no specific clinical sign could be found, a diagnosis of fungus ball is frequently made after a long term symptomatic period. CT scan findings of metallic or calcified densities within an opacified sinus cavity are highly suggestive of a fungus ball, but mycological and histological studies are essential to confirm the diagnosis. Treatment consisted of functional endonasal sinus surgery and was successful in 172 out of 173 cases.

Keywords Chronic rhinosinusitis, fungus ball, aspergillosis, fungal sinusitis, *Aspergillus fumigatus*

Introduction

The incidence of fungal rhinosinusitis in the immunocompetent population has been increasing over the past decade. Several different clinical presentations can be distinguished, including acute and chronic invasive fungal infections, as well as non-invasive fungal sinusitis including fungus ball and allergic fungal sinusitis [1–3].

In France, fungal balls are the most frequent non-invasive mycologic sinusitis reported [4–6]. Its incidence, prevalence, as well as its risk factors are still unknown. However, the presence of dental paste in the maxillary sinus has been put forward as a factor involved in this infection [7–9]. The clinical presentation of fungus balls is non-specific and asymptomatic cases have also been observed [5,7]. The endoscopic nasal examination is usually normal but oedema or purulent secretion may be observed [5,7]. The typical computed tomography (CT) scan presentation may include heterogeneous opacities associated with discrete calcification or metallic densities within the involved sinus cavity [10]. The maxillary sinus is the most

Received 26 December 2004; Accepted 17 June 2005
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DOI: 10.1080/13693780500235728

common location described in the English literature followed by the sphenoid sinus [6,7]. *Aspergillus fumigatus* is the most frequently encountered etiologic agent of fungus balls in France [5,6]. More rarely, *Scedosporium apiospermum* and *Aspergillus flavus* have been identified as the cause of infections [5,6,11]. The diagnosis is suggested by histopathological analysis, and confirmed through fungal culture [1,7].

The authors analyzed the epidemiological data of the 173 patients diagnosed with fungus ball involving one or more sinus cavities confirmed by mycology and/or histological exams. Epidemiological data, clinical presentation, CT scan data, mycological and histological results are discussed.

Materials and methods

The current retrospective series from a single university medical center (from 01/01/1989 to 12/31/2002) was based on the retrospective review of the medical files, the operative charts and the histopathological reports of 173 consecutive patients diagnosed with paranasal sinus fungus balls confirmed by histopathology and mycological analysis. A review was undertaken of all patient information including age, gender, geography, previous surgery, previous dental care, location of infection, nasal endoscopy and CT scan results. Histopathological examination were performed on fungus balls with Gomori methenamine silver staining and showed numerous entangled hyphae with 45° branching. Mucosa biopsy was performed only in cases in which the fungal etiology were in doubt (N = 20). Mycology examination consisted of direct smears to observe filamenteous fungi and fungal culture on Sabouraud dextrose agar medium (Bio-Rad, Marnes La Coquette, France), with or without chloramphenicol (Bio-Rad), incubated at 27°C and 37°C for 3 weeks. Galactomannans were detected in 34 cases in the supernatant of mashed fungus ball with the Platelia *Aspergillus* kit [12]. The latter consists of an immunoenzymatic sandwich microplate technique using rat monoclonal antibody EBA2 (sensitivity limit, 1 ng/ml). In addition, the Pastorex *Aspergillus* kit, involving an agglutination technique using latex particles coated with monoclonal antibodies (sensitivity limit, 15 ng/ml) was employed in 34 cases.

Results

Epidemiology and clinical presentation

All patients were clinically healthy and none had had any previous or concomitant history of pulmonary aspergillosis. The gender, age distribution, and living area of the patients are presented in Table 1. Four patients were clinically identified as asthmatic and 23 as atopic.

As depicted in Table 2, most patients suffered from purulent nasal discharges, facial pain and chronic nasal obstructions. Endodontic treatment with intracanal or dental fillings was found in 131 out of 173 patients but homolateral overfilling was suspected in only 18 cases (10.4%). The distribution of fungus balls within paranasal sinuses among the 173 patients is presented in Tables 3 and 4. Pre-operative nasal endoscopy performed on all patients, revealed a swelling of the mucosa and purulent nasal discharges for 76 and 73 patients, respectively. The remaining 29 patients had a normal nasal endoscopy. None of the patients received preoperative oral or topical nasal steroids.

Radiology results

CT scans were performed on 92% (159/173) of the patients and various opacities were observed (Table 5). The results ranged from isolated sinus opacification, with or without discrete calcification or metallic densities (Figs. 1 and 2), to a pseudotumor appearance (Fig. 3). The most common observation (80%) was a completely opacified sinus cavity containing calcification or metallic densities surrounded by spiculated or linear microcalcifications. This was followed in frequency by a thickening of the walls of the involved sinus (Fig. 4). Evidence of bone erosion or remodeling was present in 4 patients.

Histopathology and mycology

The surrounding connective tissue demonstrated large areas of interstitial inflammatory mononuclear cells, including lymphocytes, plasma cells and/or mastocytes. In contrast, very few scattered periglandular eosinophils were observed. No invasion of the mucous

Table 1 Characteristic of 173 patients

Gender (Nb)	
Male	69
Female	104
Age	
Mean (Year)	49
Range (Year)	14–87
Mean age for maxillary sinus involvement (Year)	47
Mean age for sphenoid sinus involvement (Year)	51
Area living (Nb)	
Rural area	120
Urban area	53

Table 2 Symptoms reported by the patients suffering from fungus balls (all localizations included)

Symptoms	*N*
Purulent nasal discharge	88 (50.8%)
Facial pain	64 (37%)
Chronic nasal obstruction	54 (31.2%)
Post nasal discharge	25 (14.4%)
Asymptomatic	18 (10.4%)
Chronic cough	10 (5.7%)

membranes were noted in histopathology studies of the 20 patients who had had mucosa biopsies. Direct smears were positive for filamenteous fungi in 115 cases and fungi were recoved in culture in 50 cases, i.e., *A. fumigatus* (45 cases), *S. apiospermum* (4 cases) and *A. terreus* (1 case). Positive cultures have always been associated with direct positive smear or histological examination. In 4 cases, histology and direct smear were negative but the diagnosis of fungus rhinosinusitis was made because of the clinical aspect of the fungus ball. Galactomannans was detected in 28 out of 34 cases.

Discussion

A fungus ball of the paranasal sinuses is defined as a non-invasive fungal rhinosinusitis occurring in the immunocompetent host [7,8]. The diagnosis is primarily based on histopathology findings as fungal cultures are frequently negative [5]. In France, the first published case is attributed to Plaignaud in 1791 [13], while in the English literature, Mac Kenzie [14] was the first to describe a case of non-invasive fungal sinusitis. Since these first reports, there have been several other cases described in Europe and the United States [5–7,15,16].

Epidemiology

The large number of cases encountered in our region, located in the western part of France, is likely due to multiple factors including the fact that we are a tertiary referral center for sinus diseases. Nevertheless, according to the international literature [5,7,15], populations in certain geographic regions are more susceptible to developing this type of non-invasive pathology in contrast to other areas where invasive or allergic fungal rhinosinusitis is more frequently observed [2,17]. As in our previous series which included 53 cases from our institution, as well as in other reports [5,7,18], older individuals appear to be more susceptible, with an average patient age of 49 years. The age of patients in this study ranged from 14 to 87 years, with the youngest case being a 14 year-old girl who was already pubescent. Females were predominant in our studies (60.1%) These results are similar to the multicenter series published by Barry [18] (mean age 48.3 ± 15 years; extreme 15 years to 90 years) but the age bracket is lower than for the other series previously reported [7]. Ferguson [7] suggests that the higher female representation may be due to the older population and the longer life expectancy of women in Western populations. However, our younger population does not seem to support this hypothesis. No specific risk factors have been found (respiratory allergy, diabetes, asthma). In France, the study [19] of the composition of the ambient air highlights the absence of dematiaceous fungi compared to what can be found in reports from the USA.

Table 3 Paranasal localizations of fungus balls

Paranasal localizations	*N*
Maxillary sinus (unilateral)	136 (79%)
Maxillary sinus (bilateral)	7 (4%)
Sphenoidal	17 (10%)
Ethmoidal	6 (3.4%)
Pan sinusal involvement	3 (2%)
Frontal	2 (1.1%)
Concha bullosa	2 (1.1%)
Total	173 (100%)

Table 4 Paranasal localizations of fungus balls diagnosed each year between 1989 and 2002 at the University care center

Years	Maxillary sinus (unilateral)	Maxillary sinus (bilateral)	Sphenoid	Others	Total
2002	12	2	1	1	16
2001	8	1	3	2	14
2000	9	1	3	2	15
1999	14	0	0	1	15
1998	11	1	1	2	15
1997	10	0	2	0	12
1996	15	0	1	0	16
1995	13	0	2	2	17
1994	13	0	1	2	16
1993	19	0	1	1	21
1992	2	1	2	0	5
1991	4	1	0	0	5
1990	4	0	0	0	4
1989	2	0	0	0	2
Total	136	7	17	13	173

Table 5 CT scan findings of 159 patients

Heterogeneous opacities	*N* = 132/159 (83%)
Homogeneous opacities	*N* = 27/159 (17%)
Metallic density	*N* = 97/159 (61%)

Fig. 1 Computed tomographic scan. Axial view showing a bilateral maxillary sinus fungus ball (*Aspergillus fumigatus*) without involvement of other sinus cavities.

Pathogenesis

The pathophysiology of fungus ball remains unknown despite previous reports suggesting the overfilling of dental cavities as a risk factor [9]. In this study such overfilling was present in only 18 of 173 cases. Furthermore, in our series, the presence of 7 cases of bilateral maxillary sinus fungus balls without any involvement of other sinus cavities, does not support this hypothesis. In such cases, it is also difficult to pinpoint a specific local factor such as anatomic variations of the middle meatus. The maxillary sinus and the sphenoid sinus were the most frequent locations encountered. This finding leads us to exclude the hypothesis of direct aero-contamination through the sinus ostium because the sphenoid sinus would be more frequently infected due to the position of its ostium. We did not find, as also indicated by Barry [18], environmental factors that might have contributed to the infection [19,20]. To our knowledge, the only factor, common to all series, is that fungus balls have never been encountered in children before puberty.

Fig. 2 Computed tomographic scan. Coronal view showing a heterogeneous opacity with metal dense foreign body of the right maxillary sinus cavity.

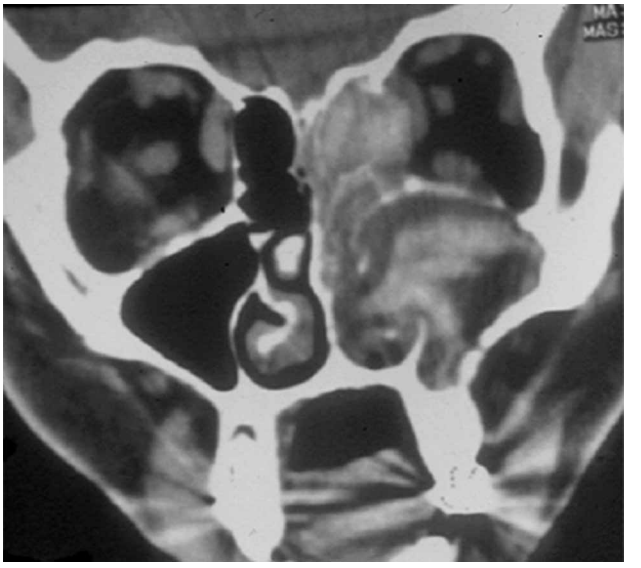

Fig. 3 Computed tomographic scan. Coronal view showing a pseudotumoral appearance of the left maxillary sinus cavity.

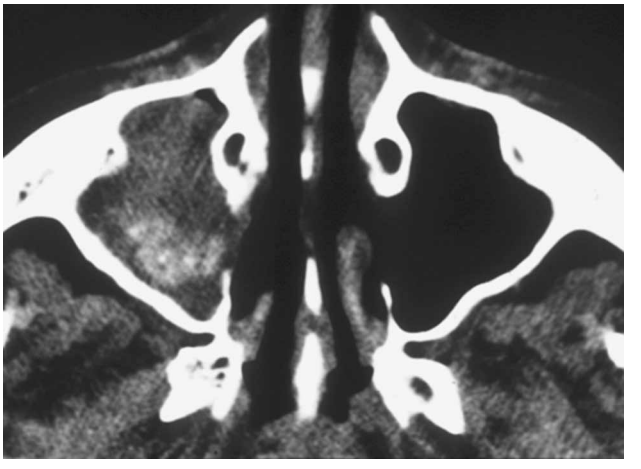

Fig. 4 Computed tomographic scan. Axial view showing micro-opacities and a thickening of the walls of the right maxillary sinus cavity.

Clinical presentation

The symptoms of fungus ball in this group of patients are not specific, with chronic nasal discharge, nasal obstruction and less commonly pain as reported by Ferguson [7] and DeShazo [1]. In our experience, sphenoid involvement has always been symptomatic as reported by Nicolai [21]. In contrast, a fungus ball located in the maxillary sinus may be totally asymptomatic [18] as it was in 18 cases (10%) in this study. No complications were observed. Nasal endoscopy was not specific, with findings ranging from completely normal mucosa to swelling or purulent discharge associated with edema or polyps.

Radiology appearance

A CT scan was essential in the assessment of these infections. In our series, the CT scan results ranged from an isolated, unilateral sinus opacification to diffuse sinus involvement with bone erosion and orbital expansion (Fig. 5). The extent of bone remodeling including erosion or thickening is likely associated with the degree of inflammation of the mucous membrane surrounding the fungus ball as in chronic inflammatory sinusitis and after endonasal surgical treatment [5,22]. Spontaneous bone reconstruction was in almost all cases observed a few months after the complete removal of the fungus ball. Metal dense body images have been attributed to zinc oxide from overfilled dental cavities [9] or metal ions deposited within necrotic areas of the mycelium [15] but it is also seen in non-fungal maxillary sinusitis [4]. Nevertheless, we also think that in cases of maxillary sinus opacification, discrete intrasinus calcifications or metallic densities are highly suggestive of a fungus ball [4].

Fig. 5 Computed tomographic scan. Coronal view showing a bone lysis and orbital expansion of the right maxillary sinus cavity.

Immunology

In this study, all patients were considered clinically immunocompetent as based on blood count evaluation. Total or specific anti-*Aspergillus* IgE studies and immunological explorations were not conducted systematically for all the patients included in the study. In sinuses, the local immunity is very developed and a complete immunology investigation will be normal.

The incidence of asthma and atopy among our study group was similar to the general population. For all patients with sphenoid or pansinus involvement, as well as pseudotumor appearances on CT scans, no abnormalities were found confirming the diagnosis of non-allergic and non-invasive fungus balls [8].

Histopathology

In all our cases, samples of the fungus ball and of the surrounding mucous membrane were examined histologically. The use of different specific stains (e.g., Grocott's methenamine silver) in this exam, as noted in other publications, was considered as the most sensitive (93.6%, 162/173) [5–8,15]. As previously reported in the literature [5,7,15,23], *Aspergillus* spp. have been the most frequently suspected agents (Fig. 6), but mycological examinations [2,8] were necessary for a positive identification of the fungal species.

Mycology

Only 32.1% (50/156) of the cultures were positive in this series which is in line with other reports and could be attributed to the poor viability of the fungi [7,15]. As noted in Table 6, the histopathological examination is more sensitive (93.6%) than fungal cultures (32.1%). The diagnosis of fungus ball was performed through

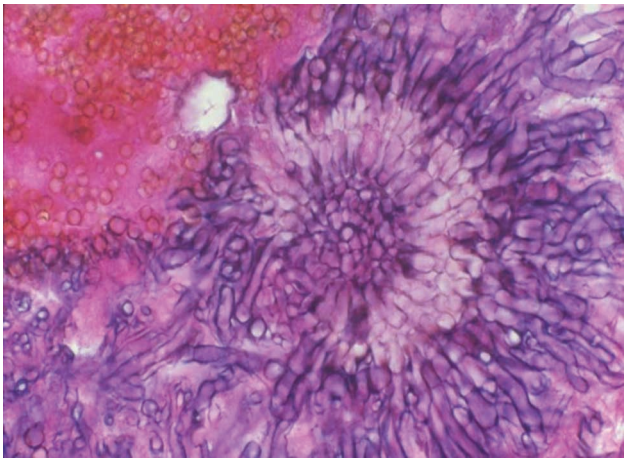

Fig. 6 *Aspergillus fumigatus* in fungus ball.

clinical and CT scan examinations. In those instances in which a fungus was recovered, *A. fumigatus* was the most common agent encountered [5,6,22,24]. According to the air composition in our region [19], the reason for this high proportion is not known since other fungal species are also represented in the ambient air around the patients [19,20].

In our series, *S. apiospermum* was the second most commonly isolated fungus without specific sinus localization and *A. flavus* may also be responsible for fungus ball formation, but mainly in specific geographic areas [6]. Studies like PCR can help the diagnosis and identify precisely the causal agent [16].

Treatment and evolution

All patients were treated with endoscopic endonasal surgery, the technique used depending on the localization (middle antrostomy, sphenoidotomy, ethmoidectomy). Asymptomatic patients were also treated but they were referred to eliminate any risk of infection before cardiovascular or orthopedic surgery. There were no complications. No local or general antifungal treatment was associated in any of the reported cases since we dealt with a non invasive fungal sinusitis.

All the patients were considered cured with a mean follow up of 7 years except for one case for whom a relapse was observed 3 years after the first surgical procedure.

Conclusions

The fungus ball is becoming the most common form of unilateral chronic infectious rhinosinusitis in the adult population in France. In our experience, the incidence is around 20 cases per year. This may be due to a better awareness and recognition of this clinical entity, as well as other, as-of-yet unknown environmental factors. The diagnosis is frequently made after a long term symptomatic period since there are no specific clinical indicators. CT scan findings of calcifications or metallic densities within an opacified sinus cavity are highly suggestive of fungus balls. However, histological and mycological assessments are essential to confirm the diagnosis, with histology being more accurate than mycological investigations. Further studies are needed to get a clearer understanding of the true incidence, without forgetting the risk factors as well as the prevention of this particular pathology in the healthy population.

Table 6 Comparison between histopathology, mycological direct smear and fungal culture of the fungus ball collected

	Histology positive	Histology negative
Direct smear		
Positive	108	7
Negative	32	4
Indeterminate*	22	0
Fungal culture		
Positive	45	5
Negative	100	0
Indeterminate*	23	0

*Data not collected for these patients

Acknowledgements

We are thankful to Edwin Ishoo MD, Assistant Professor, Department of Otolaryngology-Head & Neck Surgery at the University of Illinois, Champaigne, Illinois, USA, for his help in preparing the manuscript and to Alain Gardrat Principal Lecturer at the University of Poitiers for supervising the translation.

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