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Fungus-like sinusitis

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Abstract. *Fungus-like sinusitis. Fungus-like sinusitis* is also called *eosinophilic mucin rhinosinusitis (EMRS)*. This terminology is purely descriptive and refers to a rhinosinusitis, whose clinical presentation and imaging are similar to those of a noninvasive fungal sinusitis but in which fungus could not be demonstrated pathologically using the conventional silver staining technique or on culture.
The authors report 2 clinical cases and recall the diagnostic criteria for the different forms of fungal sinusitis in immunocompetent patients.

Introduction

Fungal sinusitis usually presents as a symptomatic, often painful, chronic sinusitis that is resistant to medical therapy, thus making surgical intervention necessary.[1] It affects both immunocompromised and immunocompetent patients.[2] In the latter, it is an extramucosal and noninvasive fungal sinusitis, in which the fungal hyphae are present in the lumen of the involved sinuses and not in the sinus mucosa nor in other tissues.[3] The purposes of this paper are to report 2 cases of *fungus-like sinusitis*, also called *eosinophilic mucin rhinosinusitis (EMRS)*[4] and to define the diagnostic criteria for this clinicopathological entity and to recall those for the different forms of extramucosal fungal rhinosinusitis.

Case reports

Case 1

A cachectic 56-year-old woman was hospitalized for parenteral nutrition because of a short bowel syndrome. She had had a partial colectomy for doligocolon and a wide resection of the small intestine secondary to a mesenteric infarction. She took prednisolone (Deltacortril®) 7,5 mg/d, sulfasalazine (Salazopyrine®) 4 × 500 mg/d, omeprazole 10 mg/d, calcium (Calcium Sandoz®) 3 × 500 mg/d, vitamin D (Steovit®) 2 × 400 mg/d and folic acid (Folavit 4®) 1 tablet per day. A computed tomography scan (CT scan) of the head and neck for evaluation of a bilateral swelling of the parotid glands demonstrated a benign homogeneous hypertrophy of the parotids and also a total opacification of the right maxillary sinus with sclerosis of its bony walls. The bony walls of the single sphenoid sinus, particularly the anterior one, were expanded and eroded, (Figures 1 and 2). A magnetic resonance (MR) imaging displayed a diffuse and regular hyperplasia of the sinus mucosa that enhanced after injection of Gadolinium®. The centre was hypo-echogenic on both T_1 and T_2 weighted sequences. Nasal endoscopy revealed greyish concretions extruding from the right superior meatus.

A diagnosis of fungal maxillary and sphenoid sinusitis was made and the patient was referred to the ENT department for surgery. A right middle antrostomy under endoscopic guidance and a bilateral sphenoidotomy through a paraseptal approach was performed. Compact concretions were extirpated from the maxillary and the sphenoid sinuses (Figure 3). Histopathologic examination revealed a dense mucoproteinaceous material with some Charcot-Leyden crystals. There were some eosinophils at the margins of the specimen. Calcofluor, PAS and Grocott's silver stains were negative. Cultures did not yield bacteria or fungi. Allergic skin tests were negative for aeroallergens (house dust mites, grass pollens and moulds). These data were not consistent with the diagnosis of fungal sinusitis but rather

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Figure 1
Axial CT showing total opacification of the right maxillary sinus, a radiodense body and sclerosis of the sinus walls.

Figure 2
Axial CT-bulging and partial erosion of the anterior wall of the sphenoid sinus – Sclerosis of the sinus walls-radiodense area.

with the clinicopathological entity termed *eosinophilic mucin rhinosinusitis (EMRS)*. The postoperative outcome was uneventful. No antifungal agent was prescribed but nasal steroids were used for 6 weeks postoperatively.

Case 2

An 18-year-old woman presented to the ENT consultation with frontal pain and a post nasal drip. Her past medical history was negative and she had no history of facial trauma or allergy. The clinical examination (anterior rhinoscopy and nasal endoscopy) was unremarkable but a sinus CT scan showed total opacification of the right frontal sinus. The intersinus septum seemed to bulge on the left side. An area with a radiodense body was seen (Figure 4). There was no concomitant ethmoidal sinusitis. The patient underwent an endonasal bilateral anterior ethmoidectomy with resection of the intersinus septum. White, inspissated and sticky secretions were aspirated from the right frontal sinus (Figure 5). Calcofluor stain and cultures were negative.

Histopathologic examination displayed an acellular matrix with some calcifications (Figure 6). No neutrophils, eosinophils, Charcot-Leyden crystals or fungal elements were visualized. The definitive diagnosis was a *fungus-like sinusitis*. The postsurgical outcome was good.

Discussion

In immunocompetent patients, the most important forms of noninvasive fungal sinusitis are the *Fungal ball* and *Allergic Fungal Sinusitis* (AFS).

A) The *fungal ball* (mycetoma) is the commonest form of extramucosal fungal sinusitis.[5] It is characterized by a dense and compact conglomerate of fungal hyphae lying on the sinus mucosa, which is infiltrated by lymphocytes and plasma cells. In decreasing order of frequency, it involves the maxillary, the sphenoid, the ethmoid and finally the frontal sinus. It is found in healthy, non-atopic adults with a slight female predilection. A prior history of sinus disease, trauma, or a foreign body may be present.[6] Sinus CT scan typically shows a unilateral, partial or complete opacification of one or more sinuses and sclerosis of the sinus walls.[7] Radiodense foreign bodies are seen in 60% of the cases. In the other, there is only variable unilateral hyperplasia of the mucosa. Surgical debridement is the mode of treatment and in most cases, this is performed endonasally under endoscopic guidance.

B) *Allergic Fungal sinusitis* (AFS) is the other form of fungal sinusitis affecting immunocompetent patients. In 1981, Millar *et al.*[8] was the first to report 5 cases of Allergic Aspergillosis of the maxillary sinus but it was Katzenstein *et al.*[9] who proposed the concept of Allergic Aspergillus Sinusitis (AAS) in 1983 by presenting a

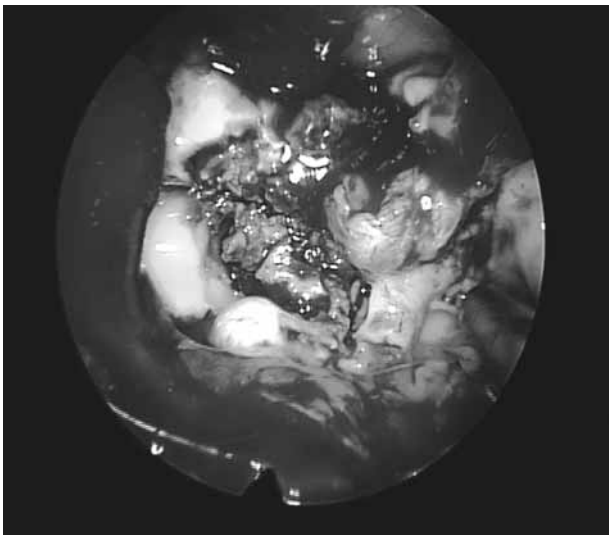

Figure 3
Intra-operative view of black and cheesy concretions in the sphenoid sinus – Similar findings in the maxillary sinus.

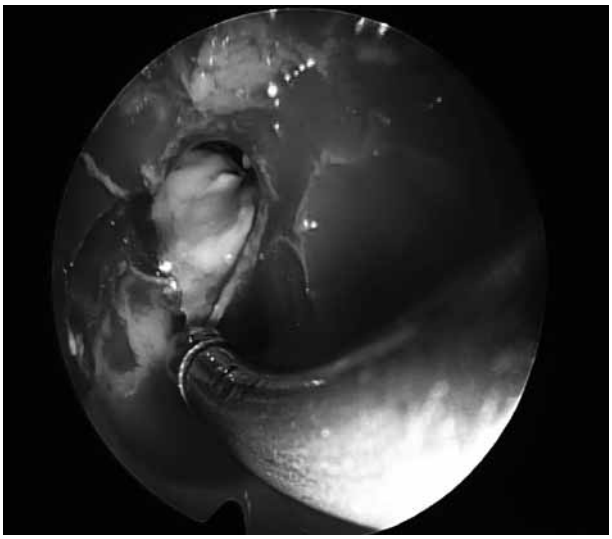

Figure 5
Intra-operative view – white sticky secretion aspirated from the right frontal sinus.

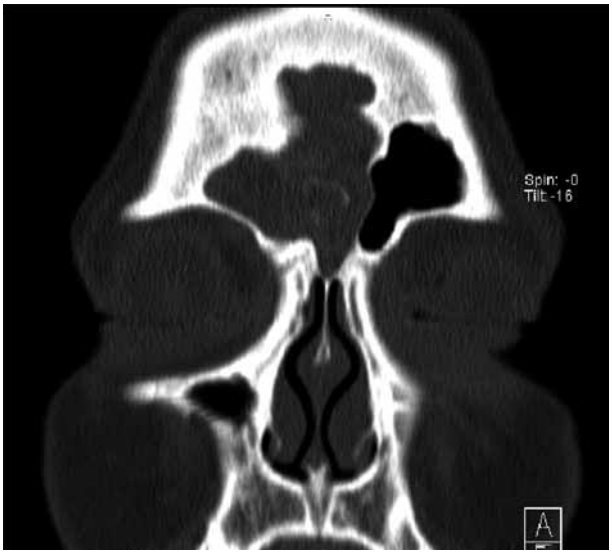

Figure 4
Sinus CT scan – coronal view
Total opacification of the right frontal sinus-bulging of the intersinus septum-radiodense body.

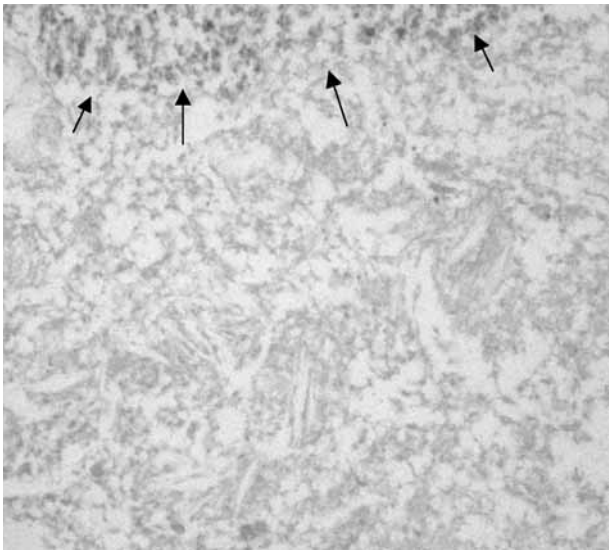

Figure 6
Light microscopy – low magnification – PAS staining.
Eosinophilic acellular matrix with microcalcifications (→).

cohort of 7 young adults with asthma and operated upon for chronic sinusitis or nasal polyposis. The histopathologic findings were similar to mucoid impaction, which is commonly associated with Allergic Bronchopulmonary Aspergillosis (ABPA). As mycological studies yield Aspergillus species in less than 15% of the cases[10] and demonstrated black fungi of the Dematiaceous genera such as Bipolaris, Curvularia, Dreschlera, Alternaria,[11] in 1989 Robson *et al.*[12] proposed the term *Allergic Fungal Sinusitis* (AFS). As the levels of the serum IgE antibodies specific for fungi are elevated in only 50% of the cases, more recently Ponikau *et al.*[13] proposed the term *Eosinophilic fungal Rhinosinusitis* (EFRS).

The difference between *AFS* and *EFRS* is that AFS usually implies an IgE-mediated allergic reaction documented by allergic skin tests or elevated specific IgE

Table 1

Diagnostic criteria for allergic fungal sinusitis

– Chronic rhinosinusitis with or without polyposis
– Presence of allergic mucin
– Demonstration of fungal hyphae in allergic mucin by direct microscopy or special stains
– Absence of tissue invasion histologically

to fungi. The diagnosis is based on the identification of an *allergic mucin* and *fungal hyphae*.[14] Table 1 summarizes the diagnostic criteria for *allergic fungal sinusitis*.

Grossly, *allergic mucin* consists of brownish-green, inspissated, thick and viscid material of a peanut butter-like consistency lying interspersed between the nasal or sinus polyps. Its microscopic characteristics consist of layered mucus, clumps of cells, chiefly eosinophils (many of which are necrotic) and Charcot-Leyden crystals. Fungal hyphae are scanty and scattered, lying loosely amongst the mucus layers. Their identification requires a high index of suspicion by the pathologist and specific staining techniques.[15,16]

In adults, the clinical presentation consists of a severe nasal polyposis or chronic sinusitis resistant to medical therapy and recurring after surgery. Asthma is present in up to 50% of the cases. The disease is often bilateral but many cases are unilateral resembling a paranasal sinus tumor.[12,17-19]

In children the disease is more often associated with facial deformity, diplopia, telecanthus, exophthalmia or neurological symptoms such as headache. These are caused by the expansion of the pathology towards the orbit and/or the anterior cranial fossa.[20,21]

Sinus computed tomography scan displays an heterogeneous opacification of the sinus(es) with areas of high attenuation and increased density.[22] Changes of the bony walls are noted in about 20% of the cases. They consist of displacement (bulging), erosion or even dehiscence.[23]

On MRI, the signal intensity is variable. Typically the centre of the lesion is hypointense on T1 and T2 weighted sequences whereas the rim is hyperintense and enhances after injection[19,24] of Gadolinium®.

The exact pathogenesis is unknown but it has been proposed that the eosinophilic disease of AFS is driven by a type I or a type III hypersensitivity to fungal antigens contained and growing in the mucin.[25]

Management combines surgery and low-dose corticosteroid therapy. Surgery must exenterate all the concretions from the sinus cavities. The inflammatory mucosa does not need any radical extirpation. Corticosteroids are then required to reduce the underlying inflammatory (allergic) reaction.

C) In the cases reported here, the clinical presentation and imaging were highly suggestive of one form of noninvasive fungal sinusitis. In the first case, a fungal ball was suspected based on the CT scan findings and the macroscopic view of the material present in the maxillary and the sphenoid sinuses. In the second case, calcifications on the CT scan also suggested a fungal ball but the sticky and mucoid consistency of the secretions was more consistent with the diagnosis of an eosinophilic fungal rhinosinusitis. Nevertheless, fungal elements were not identified both on histopathology and on culture leading us to call this entity a *fungus-like sinusitis.*

Other similar cases have been reported. Ferguson *et al.*,[4] Katzenstein *et al.*,[9] Cody *et al.*,[10] Allphin *et al.*,[26] Ramadan *et al.*,[27] Perez *et al.*[28] and Lara *et al.*[29] reported respectively 29, 2, 19, 11, 4, 4 and 10 cases. This entity was called *allergic mucin but without fungal hyphae*,[26] *AFS-like syndrome*,[10] *allergic mucin sinusitis without fungus*[27] or e*osinophilic mucin rhinosinusitis* (EMRS).[4] All these terminologies refer to a rhinosinusitis whose clinical presentation and imaging are similar to a noninvasive fungal sinusitis but where the histology did not identify the fungus.

This raises the question whether AFS and EMRS are 2 different or a single entity. Katzenstein *et al.*,[9] Ramadan *et al.*,[27] Lara *et al.*,[29] Ponikau[1] *et al.*[6] and Rupa *et al.*[15] concluded that no significant differences existed between the two groups and that the absence of fungal elements was attributed to a sampling error.

Cody *et al.*[10] and Ferguson[4] considered the 2 entities to be different. Based on a large review of the English-language literature and his 42 cases, Ferguson stated that the two entities, while overlapping on clinical and immunological examination, are significantly and statistically different. He demonstrated that EMRS patients as compared with AFS patients were significantly older (mean, 54y vs. 34 y, respectively), were more frequently asthmatic (84% vs. 28% respectively) and tended to have a higher incidence of aspirin sensitivity (37% vs. 20%, respectively).

Total IgE levels were elevated in both entities but are significantly higher in AFS. IgG and IgG1 deficiencies in EMRS were common but are seldom reported. Finally EMRS was exclusively a bilateral disease whereas AFS can be unilateral and localized.

The discussion is ongoing but obviously the cases reported here do not support all Ferguson's conclusions. In this series EMRS affected a young adult and was not associated with nasal polyps, asthma and aspirin sensitivity. The disease was not bilateral but involved one or 2 sinuses unilaterally. Surgical debridement alone was effective without use of long term nasal steroids. Finally the clinical presentation and imaging were identical to true noninvasive fungal rhinosinusitis.

The second question relates to the inability to demonstrate fungus on histopathology in certain circumstances. One could say that there are no fungi in the involved sinuses. Ence *et al.*[30] suggested that eosinophils present within the sinus mucin release major basic proteins, which may deteriorate in vitro or may not survive the culture process. But Ponikau *et al.*[13] demonstrated in 1999 that fungi are saprophytic organisms of the nose and the sinuses and that fungal cultures are positive in virtually all patients with chronic rhinosinusitis and also in control subjects, if special handling techniques are used and meticulous, painstaking efforts are taken to procure samples. We therefore postulate that the number of fungal organisms is so small that a sampling error may lead to false-negative results.

Rupa *et al.*[15] found more fungal elements when the tissues (nasal polyps and sinus mucosa) and allergic mucin were analyzed separately. They demonstrated that the manner in which the specimens of allergic mucin are submitted for histopathological examination is critical for visualization of fungal hyphae. The specimens should be taken during the surgery without suction, not put on gauze and taken to the laboratory immediately after the procedure. Delay in processing of the specimens leads to degradation of fungal elements. The pathologist should also be informed of the diagnosis.

Grocott methenamine-silver staining technique is still the gold standard for fungal identification but it has its limitations particularly when the amount of fungi is very low.[31]

For these particular cases, new and much more sensitive techniques are available today. These include *in situ* hybridization for ribosomal RNA,[28] the polymerase chain reaction (PCR)[32] and the technique using a fluorescein-labeled chitin-specific binding protein.[16] Unfortunately these techniques are not routinely available in all laboratories.

These recent advances in laboratory identification must be kept in mind in reviewing earlier studies on the prevalence of fungal hyphae in sinus mucus and might have some implications in the classification of the fungal sinusitis in the future.

The third question is the role and the meaning of the fungal hyphae in these entities. Are they an infectious agent, aero-allergen or saprophytic element trapped by the inflammatory and expanding process? There is no definitive answer to the question.

Management of EMRS consists firstly of surgical debridement in order to totally clear all the cavities and preserve or restore the drainage and the ventilation of the sinuses.

In the case of maxillary sinusitis a middle antrostomy is recommended, combined with an inferior antrostomy if necessary. In the case of frontal localisation, a frontomeaticotomy (anterior ethmoidectomy) enables one to aspirate the secretions from the sinuses. In the case of compact concretion, an osteoplastic flap is indicated; in the case of sphenoid sinusitis, an endonasal sphenoidotomy. In the present case, as the sphenoid sinus was single and expanded, a paraseptal approach was used. Compared to the posterior transseptal endoscopic approach, the nasal mucosal flaps were resected after the sphenoidotomy and before the resection of the posterior bony septum. This provided a wide access to the sphenoid sinuses. In the postoperative period the control of the operated cavities was easier.

Postoperatively there is no indication for systemic or topical antifungal therapy and for long term steroids because the inflammatory reaction is mild.

Conclusion

Fungus-like sinusitis is a rare entity also called *eosinophilic mucin rhinosinusitis*. It refers to a sinusitis whose clinical presentation and imaging are similar to a noninvasive fungal sinusitis but where fungal elements are not identified on culture and pathologically with conventional silver staining techniques. New and much more sensitive techniques now allow detection of fungi in almost 100% of the specimens. We predict that in the near future the presence or not of atopy will lead to the

classification of this entity into *allergic fungal sinusitis* or *eosinophilic fungal rhinosinusitis.*

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