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Eosinophilic fungal rhinosinusitis (EFRS): a distinct CT/MRI-entity? A european experience

S. Vlaminck, J. Casselman**, K. De Groef***, I. Van den Berghe***, R. Kuhweide* and S. Joniau**

*Department of Otorhinolaryngology, St-Jan General Hospital, Bruges, Belgium; **Department of Radiology, St-Jan General Hospital, Bruges, Belgium; ***Department of Anatomopathology, St-Jan General Hospital, Bruges, Belgium

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Abstract. *Eosinophilic fungal rhinosinusitis (efrs): a distinct ct/mri-entity? A european experience. Objective*: To determine the value of radiological features in the diagnosis of Eosinophilic Fungal Rhinosinusitis (EFRS).
Study design: Retrospective review of the radiological materials of 65 patients with documented Eosinophilic Fungal Rhinosinusitis treated at the same institution.
Methods: Evaluation by the ENT surgeon and the head and neck radiologist.
Results: EFRS was more common in female patients in this series. Fifty-four (83%) patients were above 30 years of age, with a peak of 18 patients (27.7%) in the seventh decade. All the patients except one (98.5%) showed bilateral mucosal thickening on unenhanced CT scans. Thirty-eight patients (58%) showed increased intrasinus attenuation on unenhanced CT scans. Thirty-seven patients (57%) showed opacification of at least one sinus; 25 (38%) showed osteitis; 11 (17%) had erosion of the sinus wall and only one patient showed minor expansion of an involved sinus. In 6 patients, typical hyperattenuation patterns on CT scans, together with distinctive MRI images, were highly suggestive of EFRS.
Conclusion: Our data show that hyperattenuation on CT images with bone window settings suggests the presence of EFRS. This hyperattenuation is more clearly seen with soft-tissue window settings. When necessary, adjunctive MRI can provide information which might be highly predictive for the diagnosis of EFRS. However, non-specific imaging findings of chronic rhinosinusitis (CRS) should also be seen as possible EFRS pathology.

Introduction

Eosinophilic Fungal Rhinosinusitis (EFRS) is thought to be a disease of young atopic people. There is little uniformity in definitions of the inclusion criteria. At one end of the spectrum, there are the minimal Mayo criteria[1] based on the histopathological absence of microscopic tissue invasion, characteristic eosinophilic mucin with fungal hyphae detectable by special staining techniques or with positive evidence of fungus. At the other end of the spectrum, there are the largely outlined clinical and pathological features as proposed by Bent and Kuhn[2] for defining the disease currently called Allergic Fungal Rhinosinusitis (AFS). Their major criteria are: (1) evidence of type I hypersensitivity; (2) nasal polyposis; (3) characteristic CT findings; (4) eosinophilic mucin; and (5) positive fungal smear, later supplemented by "or positive fungal culture". The minor criteria included: (6) asthma; (7) unilateral predominance; (8) radiographic bone erosion; (9) fungal culture; (10) Charcot-Leyden crystals; and (11) serum eosinophilia. A group of patients with some of the major and minor criteria responded so well to their treatment protocol for Allergic Fungal Sinusitis (AFS) that they are now classified as "atypical AFS patients".[2]

In 210 consecutive cases of chronic rhinosinusitis (CRS) Ponikau *et al*.[3] observed positive cultures of fungi in 96% of nasal secretions. In 93% of 101 consecutive surgical cases, histopathology and culture results confirmed the diagnosis of EFRS. The likely absence of a type I hypersensitivity in the diagnosis and the constant presence of eosinophils in the allergic mucin led them to propose the name of "Eosinophilic Fungal Rhinosinusitis" (EFRS). We will use this name throughout this article. Similar findings have been found in Europe by Braun *et al*.[4] They were able to grow fungal cultures in 91.3% of 92 consecutive patients with CRS with or

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without polyposis. Overall, the criteria for EFRS were met in 89.2% of 37 surgical cases. From a broader perspective, the existence of AFS or EFRS as distinct entities is questionable because the diagnostic criteria were used on a preselection of patients. New findings in the aetiologic understanding of chronic rhinosinusitis increasingly suggest a role for a fungal-driven inflammatory pathophysiology in chronic rhinosinusitis.[5] A recent review by Granville *et al.*[6] using adequate techniques showed a failure rate of up to 47% in clinically-diagnosed AFS patients for demonstrating fungi in the eosinophilic mucin in earlier histopathologic examinations. Recently, Ferguson[7] proposed a categorisation of the different subtypes of eosinophilic chronic rhinosinusitis: (1) superantigen-induced (S*taphylococcus* enterotoxin) ECRS; (2) allergic fungal rhinosinusitis (AFS); (3) non-allergic fungal ECRS; and (4) aspirin-exacerbated ECRS.

Currently, there are thought to be five types of sinus fungal diseases. (1) (*Fulminant) fungal sinusitis* usually occurs in immunosuppressed patients. Despite surgery and aggressive fungal therapy the mortality rate[8] is high and may reach 80%. (2) *Chronic indolent fungal sinusitis* is found in immunocompetent patients who develop granulomatous inflammation with mucosal invasion by fungal hyphae. Surgical debridement and possibly antifungal treatment are needed. This pathology is commonly found in the desert regions of Sudan.[9] (3) *Fungus ball* is a proliferation of fungal hyphae in the sinus of a non-atopic, immunocompetent host, without invasion of the mucosal lining. It may be asymptomatic and can be cured by simple debridement. (4) *Saprophytic fungal growth* can often be seen endoscopically in the sinus cavities on dried crusts and seems to have no clinical importance; it may nevertheless conceal pathologic conditions (cancer etc.). (5) *Allergic fungal rhinosinusitis* (AFRS), renamed here *Eosinophilic Fungal Rhinosinusitis* (EFRS), is the most recent type. It is typically found in immunocompetent patients of any age and sex with chronic rhinosinusitis refractory to medical therapy (antibiotics, antihistamine treatment…). Atopic condition and polyposis are frequent but not mandatory. This condition is thought to be an immunologic reaction to a variety of fungal antigens.[7] The treatment consists of surgical debridement, saline irrigations, and local and systemic steroids. Antifungal therapy is still regarded as controversial because efficacy has not yet been proven. Recent studies suggest that nasal polyposis improves to some extent in response to nasal lavages with an amphotericine B suspension.[10] The underlying mechanisms still need to be clarified, and controlled / blinded trials are indicated.[11]

Several small studies have suggested that imaging is helpful in identifying EFRS patients.[2,12] In one large study, the radiological materials of 45 patients from seven different academic institutions were reviewed by Mukherji *et al.*[13] This study aims to review the radiological findings of a group of 65 patients with proven EFRS treated at a single institution.

Methods

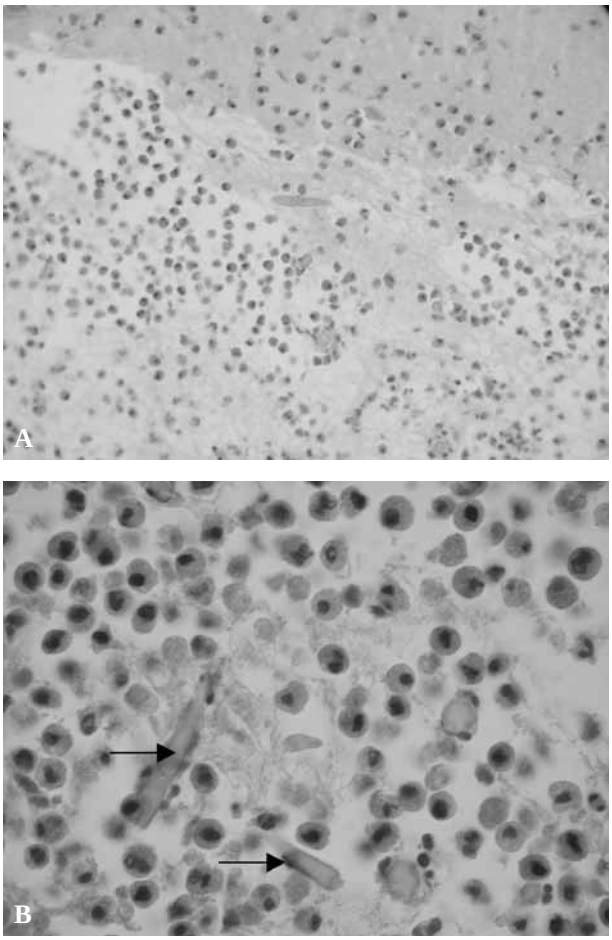
The imaging materials of 65 patients obtained between March 1993 and December 2001 were reviewed retrospectively (36 females, 29 males; age ranged from 18 to 77 years when the CT scans were made; mean age: 48.96). The diagnosis of EFRS is based on the sampling of secretions taken at surgery and in the office.

All the patients met the criteria for chronic rhinosinusitis (with or without polyposis) lasting longer than 3 months.[14] The diagnosis of EFRS was retained on the basis of

Table 1

CT findings of eosinophilic fungal rhinosinusitis

CT finding	Number of patients	Percentage
Mucosal thickening	65/65	100%
Bilateral mucosal thickening	64/65	98.5%
Involved sinus sites		
Maxillary	123/130	96%
Ethmoid	112/130	87%
Frontal	112/130	87%
Sphenoid	111/130	86%
Complete opacification of at least one sinus	37/65	57%
Increased intrasinus attenuation	38/65	58.5%
Remodeling of walls of opacified sinus	25/65	38.5%
Thinning of sinus wall of opacified sinus	11/65	16.5%
Expansion of opacified sinus	1/65	1.5%
Involvement of adjacent soft-tissue structures	0/65	0%



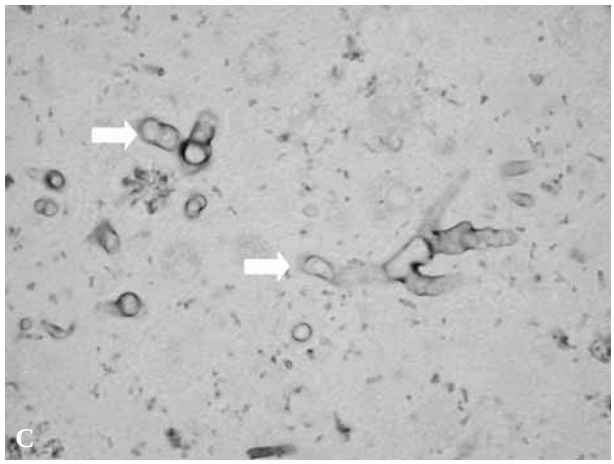


Figure 1
(A) Chronic rhinosinusitis: massive number of eosinophils in mucus ("eosinophilic mucin") (H & E stain, original magnification × 400); (B) Eosinophilic cluster with palisade formation within the nasal mucus. Charcot-Leyden crystals (black arrows), a degradation product of eosinophils, can be seen showing different cleaving patterns within the same cluster (H & E stain, original magnification × 1000); (C) Serial section from the same cluster stained with Gomori methenamine silver showing different fungal hyphae (white arrows) with different cleavage axes.

deShazo's criteria.[15] the presence of (1) CRS, (2) typical "allergic" mucin (clusters of eosinophils in layers and their by-products, e.g. Charcot-Leyden crystals), (3) fungal hyphae upon pathological examination and/or culturing (Figure 1), (4) the absence of diabetes and immunodeficiency disease and (5) invasive fungal disease. Cultures were not routinely investigated; those that were investigated were mostly negative.

Not all of the patients were fully investigated for type I hypersensitivity. The same surgeon performed endoscopic surgery in 62 cases. One patient refused revision surgery and two patients refused primary surgery.

Three patients were found to have EFRS following an endoscopic sinus operation. The first patient was operated on for a CSF leakage one year after endoscopic surgery in another institution. The second patient was operated on for a mucocele and the third patient for a left maxillary pseudotumor. CT scans, however, showed signs of CRS in all patients. Most of the patients underwent their CT scans at our institute (56/65). These basically consisted of coronal, non-contrast CT scans with bone window settings. Images were also taken in fourteen cases using soft-tissue window settings. One scan used a soft-tissue setting only. The thickness of the slices was 3 mm.

The CT findings were reviewed by the ENT surgeon and the head and neck radiologist, and were correlated with the surgical and pathological reports. The following CR signs were used to support the diagnosis of EFRS: (1) mucosal thickening, (2) the extent of sinus involvement, (3) the presence of intrasinus high attenuation areas, (4) bone expansion and thinning, (5) bone erosion and (6) the extension of disease into the adjacent soft tissues (same criteria as those used by Mukherji *et al*.[13]). The anterior and posterior ethmoid sinuses were considered to be a single complex.

The presence in some cases of minor erosive and/or remodelling disease justified eight adjunctive MRIs. CT scans taken at the time of recurrence were also investigated and correlated with the clinical findings.

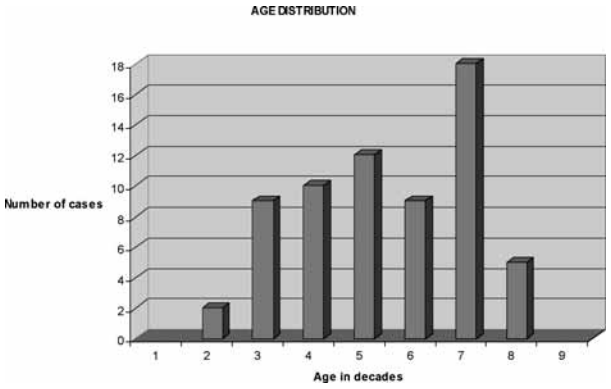


Figure 2
Age distribution in 65 EFRS patients. Peak of frequency can be observed in the seventh decade.

Results

The diagnosis of AFRS was mainly based on the collection of secretions at surgery. Endoscopic sampling was performed in three non-operated patients. Diagnosis was made prior to surgery for two other patients. However, the diagnosis could not be retained in nineteen patients (29%) since no fungi were found. It was only after recurrence that all the criteria were met, when new samples were taken which did contain fungi.

There were more female patients (36) than male patients (29). The age-distribution diagram (Figure 2) shows the age of the patients when the radiological studies were taken. Fifty-four patients (83%) were above the third decade, with a peak of eighteen patients (27.7%) in the seventh decade. The presence of an allergic background was not significantly related to the presence of EFRS.

CT findings

All the patients showed *mucosal thickening* on unenhanced CT scans. Except for one case presenting with a hemi-pansinusitis, there was bilateral involvement of the sinuses. Mucosal thickening of the maxillary sinuses was seen in 123 sinuses (96%) (63 right-sided and 60 left-sided); 112 ethmoid sinuses (87%) (56 right-sided and 56 left-sided); 112 frontal sinuses (87%) (56 right-sided and 56 left-sided) and in 111 sphenoid sinuses (86%) (52 right-sided and 59 left-sided). Thirty-seven patients (57%) had *complete opacification* of at least one sinus (29 right-sided and 30 left-sided). This opacification of at least one sinus was bilateral in 22 cases and unilateral in 15 cases. Bilateral complete opacification was observed in 2 patients and unilateral in 4 patients.The ethmoid sinuses were most commonly involved in 34 patients (52.3%) (16 right-sided and 18 left-sided). In decreasing frequency, the frontal sinuses in 28 patients (44.6%) (10 right-sided and 18 left-sided), the sphenoid sinuses in 26 patients (40%) (11 right-sided and 15 left-sided) and the maxillary sinuses in 25 patients (38.5%) (15 right-sided and 10 left-sided) were involved. *Hyperattenuation* was found in 38 cases (58%). The hyperattenuation pattern could be retained on the basis of 37 positive scans using bone window settings and one positive scan using a soft-tissue window setting despite a corresponding negative bone window CT scan. An interesting feature is that, in 13 positive scans with bone window settings, additional scans with soft-tissue settings showed those hyperattenuated regions corresponding to the eosinophilic mucin more clearly. Bilateral attenuation was seen in 25 patients and unilateral attenuation in 15 patients. Increased attenuation was seen in decreasing frequency in 33 maxillary sinuses (15 right-sided and 18 left-sided), 29 ethmoid sinuses (13 right-sided and 16 left-sided), 29 frontal sinuses (14 right-sided and 15 left-sided) and 21 sphenoid sinuses (10 right-sided and 11 left-sided). *Erosion* was found in 11 patients (17%) (8 unilateral and 3 bilateral). The infundibular complex was involved most frequently, with 7 right-sided and 5 left-sided localisations. Some minor erosion was noted at one ethmoid and one sphenoid sinus on the right side compared to 3 ethmoid sinuses and one frontal sinus on the left side. Two patients, one with a left ethmoidal mucocele and one with a left maxillary pseudotumor, were not taken into account. *Expansion* of a sinus was only seen in 4 patients. This could only be attributed to EFRS pathology in one patient. Another patient primarily underwent revision surgery for meningitis due to a left-sided anterior ethmoidal CSF-leak. Two other patients presented respectively with a left ethmoidal mucocele and a left maxillary pseudotumor. In the last three of these CRS cases, EFRS was found incidentally. *Bone remodelling* was observed in 25 patients (38%) (18 bilateral and 7 unilateral). The

posterior-lateral wall of the maxillary sinus was involved most frequently with a total number of 37 maxillary sinuses (17 right-sided and 20 left-sided), 12 sphenoid sinuses (8 right-sided and 4 left-sided), 4 ethmoid sinuses (3 right-sided and 1 left-sided) and 1 left frontal sinus. *Involvement of the adjacent structures* was not observed.

MRI findings

Additional MRIs were made in 8 of 65 cases. Expansion and remodelling were seen in three cases only. In only one case could this be attributed to EFRS pathology, and this solely on the basis of pathological examination. The two other cases related to a left ethmoidal mucocele and a left maxillary pseudotumor in combination with EFRS pathology. The remaining five cases showed some minor erosion on the pre-operative CT scan, resulting in further investigation. In all eight EFRS cases, a hypo-intense signal was typically observed on T1-weighted images and a signal void on T2-weighted images. This corresponded to the area of local surgical eosinophilic mucin concretions. In these patients, the peripheral enhancement on T1-weighted images corresponded to the inflamed mucosa in the affected sinuses.

Discussion

This retrospective review looked at more than 50 CT scans performed during the previous two years. This might reflect the more systematic collection of secretions during surgery and from outpatients leading to an increasing diagnosis of EFRS in patients with CRS with or without polyposis. It has been suggested that oral steroids could reverse the pathological features.[2]

The diagnostic criteria are often not met during the first sampling series. In this series, up to 29% (19/65) of the patients failed to meet the EFRS criteria at the time of surgery since there were no fungi upon histopathological examination. On recurrence, without any concurrent intake of oral steroids, the examination of new sampling materials met the criteria. This finding underscores the need for repetitive samplings as well as the importance of staining techniques (Figure 1). Currently, the gold standard for detecting the presence of fungal elements in the allergic mucin is the Grocott methenamine silver stain (GMS). Pathologists should be encouraged to look at eosinophils and search for scarce and destroyed/partially destroyed hyphae. Other investigators have experimented with *in situ* hybridisation for identifying the fungus.[16] However, this method is very expensive and cumbersome. Taylor *et al*.[17] recently proposed a new technique (fluorescein-labeled chitin-specific binding protein) with very high sensitivity. In this study, fungi were found in 54 consecutive patients operated on for CRS.[17] This new technique might alleviate the searching task in many ways, resulting in fewer negative histopathological results.

It seems generally accepted in the literature that the EFRS population is young and atopic.[2,18] The age diagram (Figure 2) in our series clearly shows a different pattern. Fifty-four (83%) patients were above the age of 41, with a peak of 18 patients (27.7%) in the seventh decade. Those figures might however be misleading as children are rarely operated on for CRS in our institution. Moreover, there are no routine samplings for pathological examination. Yet recently, two samples (not included) from children with CRS of unknown origin (no adenoid hypertrophy, cystic fibrosis, ciliary dyskinesia or diabetes and normal immunologic parameters) showed the typical EFRS features. This finding led us to change our approach and implement sampling procedures whenever there is purulent rhinitis or CRS pathology. The logical expectation is that more young patients with EFRS will be found in the future.

Thorough atopic screening was not conducted in this series but it is currently being undertaken. However, many of our patients do not have type I hypersensitivity (normal IgE, normal eosinophilia, negative skin testing and RAST tests) on screening. This finding favours the idea that EFRS may occur independently of type I hypersensitivity.[18]

There was a predominance of female patients (36/65) but a tendency towards an equal ratio might be expected in larger samples.[15,19]

EFRS has been recognised as a distinct clinical entity. In spite of the increasing number of reported cases and awareness, this pathology is still underestimated.

CT findings

Mucosal thickening involved the sinuses bilaterally without any marked side bias. This concurs with the findings of Mukherji *et al*.[13] Only one patient presented with unilateral hemi-pansinusitis. Within one year after endoscopic surgery the patient presented with a hemi-pansinusitis on the other side and was surgically treated.

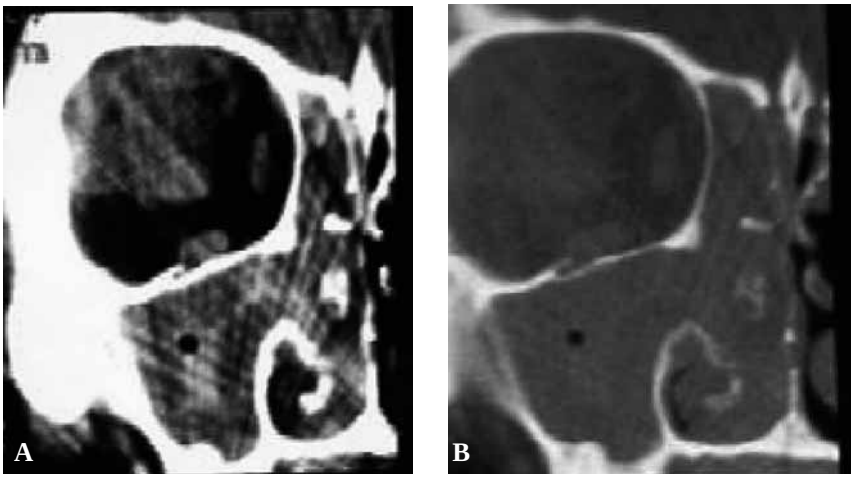


Figure 3
Coronal CT scans showing mixed densities in the sinuses. Those hyperattenuation patterns are more clearly visible on the soft-tissue window settings (A) compared to the bone window settings; (B) Those mixed densities were consistent with eosinophilic fungal rhinosinusitis.

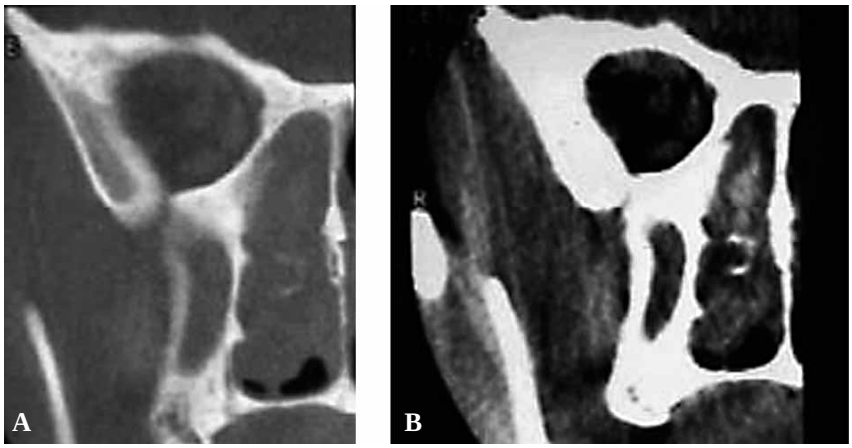


Figure 4
Coronal CT scans through the right ethmoidal sinus and upper nasal cavity of the same patient. On the bone window setting (A) a central hyperattenuation can be suspected. On the soft-tissue window setting hyperattenuation densities correspond to an eosinophilic mucin collection (B).

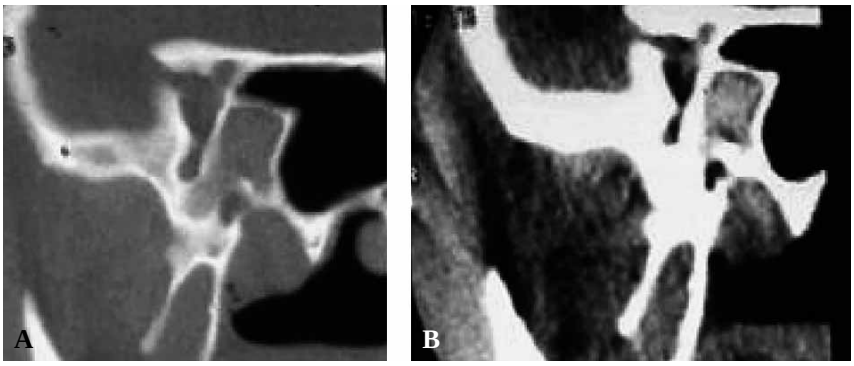


Figure 5
Coronal CT scan of right sided small sphenoid sinus demonstrates a central pattern of high attenuation on a bone window setting (A) and is more clearly seen however on the soft-tissue setting (B).Those densities are consistent with eosinophilic fungal rhinosinusitis.

In 45 patients at different institutions, Mukherji *et al.*[13] found expansion of the involved sinus in 43 patients. Forty-two patients had bone remodelling and thinning and 41 patients had erosion of the sinus wall. In a series of 10 patients, Manning *et al.*[12] found 5 patients presenting with unilateral proptosis; 9 patients had evidence of bony erosion with intraorbital or intracranial extension. Those findings suggest that the average patients in their studies were in a far more advanced stage of the disease. This could explain the rather low number of minimal erosive findings (17%) and the single case of expansive sinus found in our series. Only 37 patients in our study (57%) had at least one sinus with complete opacification, as compared to 98% in the study mentioned above.[13] We therefore assume that our patients presented at an earlier stage of the disease. Our CT findings showed hyperattenuation in 38 cases (58%), compared to 100% in the two other studies.[12,13] In 25 patients, there was bilateral hyperattenuation, with unilateral hyperattenuation being a feature in 15 patients. High attenuation was seen on the images with bone window settings in 13 patients, but was even clearer on images with soft-tissue window settings (Figures 3, 4 and 5). In one patient the hyperattenuation was only visible on the images with soft-tissue window settings. The question arises of how many more hyperattenuation patterns would have been found if imaging had taken place using soft-tissue window settings systematically. We therefore totally agree with the arguments of Mukherji *et al.*[13] in favour of soft-tissue algorithm images in CRS patients, especially where there is

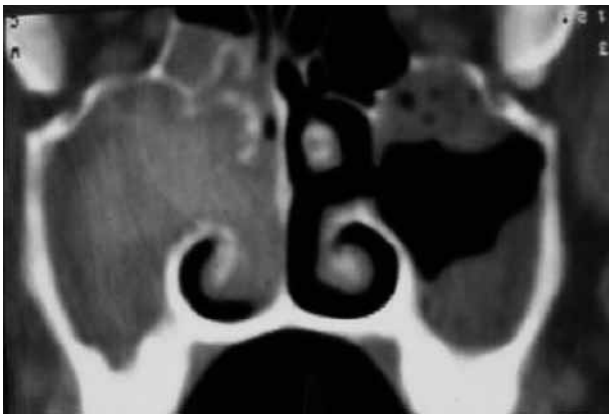


Figure 6
Coronal computed tomography scan showing the right maxillary sinus with complete opacification. Hyperattenuation is visible in the central part of the right maxillary sinus and at the bottom of the left maxillary sinus. Left sided secretions with air bubbles suggesting acute inflammation. At surgery, secretions of both sides were consistent with eosinophilic fungal rhinosinusitis.

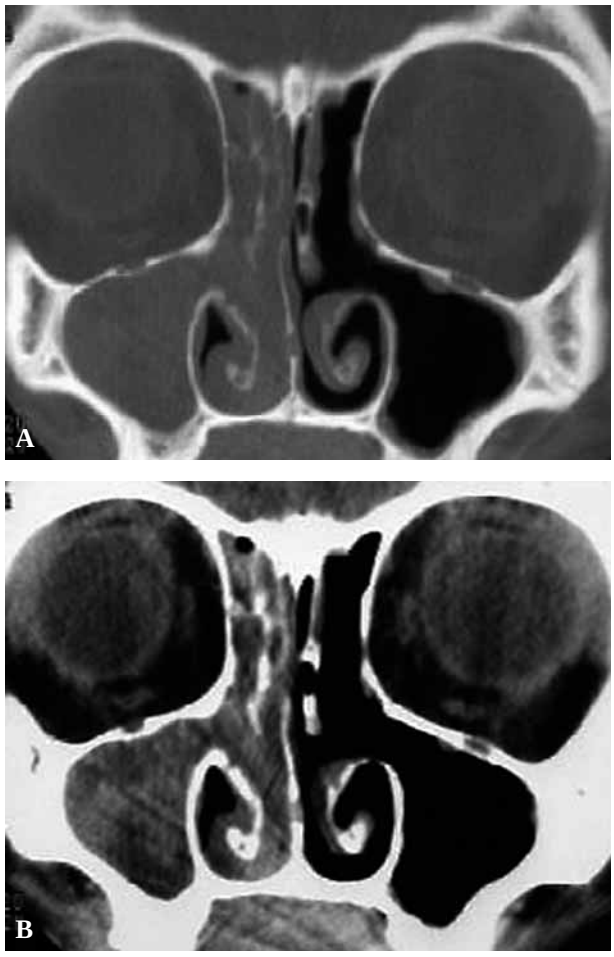


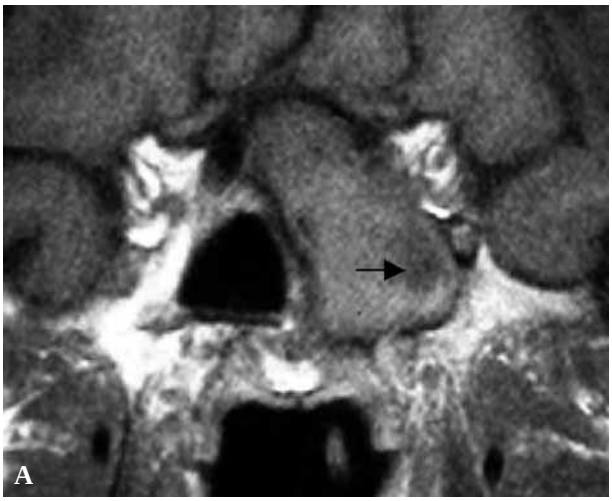
Figure 7
Coronal CT scans showing a hemi-pansinusitis recurrence after previous bilateral endoscopic surgery. The mixed densities are hardly visible on a bone window setting (A) compared to the mixed densities on a soft tissue window setting (B). The pathologic findings at surgery were consistent with recurrence of eosinophilic fungal rhinosinusitis.

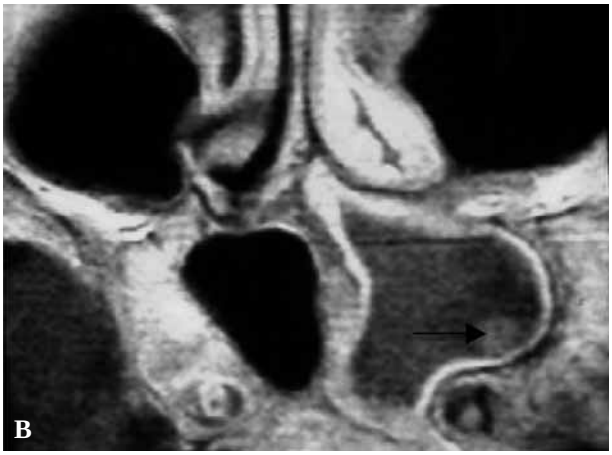
total opacification. In these cases, hyperattenuation patterns are more likely to be found.[13,18]

An important feature of this series was that eosinophilic mucin was not only found in hyperattenuated sinuses. Sinuses that were still well aerated upon CT scanning were found to contain thin layers of eosinophilic mucin at surgery (Figure 6). This finding suggests that thin layers or small amounts of mucin are not always detectable by CT scan and that their presence cannot therefore be excluded, as stated by Ponikau *et al*.[3] Moreover, in operated patients seen during early recurrence, it was possible to find layers of secretions upon endoscopy.

Hyperattenuation is considered to be the result of the accumulation of heavy metals (iron and manganese), calcium and inspissated secretions.[20,21] In our experience this statement applies more to fungus balls, as outlined by Stammberger *et al*.[21] It is essential to stress that EFRS pathology is not based on a proliferation of fungi in contrast with a fungus ball. The latter can be found in slowly evolving fungal masses (asymptomatic for many years), typically affecting one isolated sinus. The clinical observation of recurrences in EFRS sometimes suggests a very rapid onset of disease with inspissated secretions in the early stages. Logically, in most of our patients with recurrent disease, the cellular debris resulting from the necrosis of eosinophils was the only explanation for the radiological hyperdensities (Figure 7). Further investigation of eosinophilic mucin is required to prove this statement. We agree with Schubert[18] that contrasting or hyperattenuation features are a common finding in EFRS.

In this series, however, 17 patients (42%) presented with atypical CT scans of CRS without any sign of hyperattenuation. This figure could have been lower if, as stated above, soft-tissue window settings had been used systematically. Those findings demonstrate





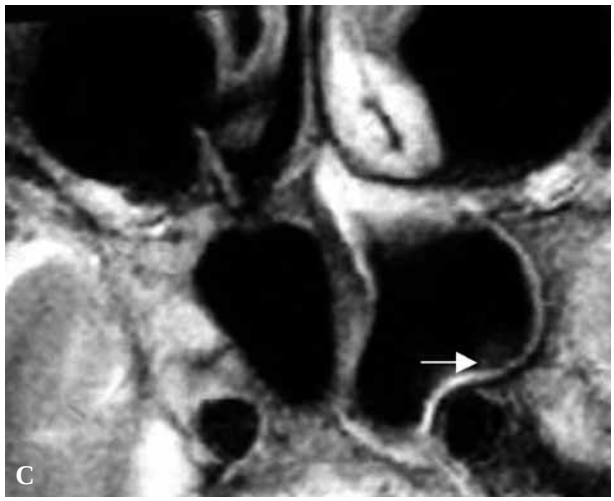
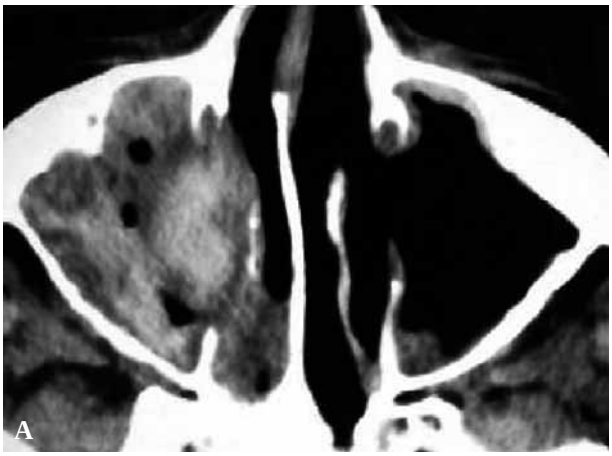


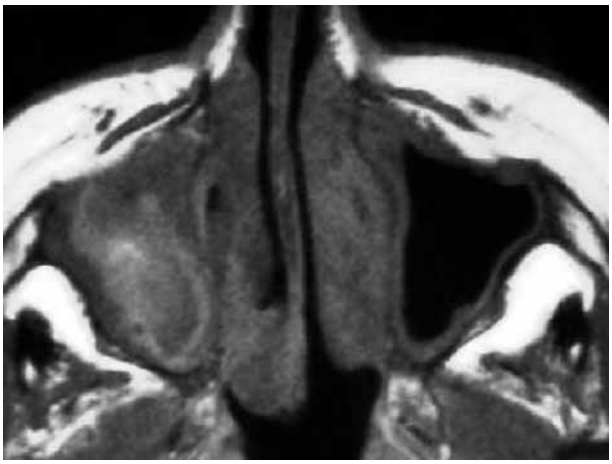
Figure 8
T1-weighted MRI in coronal view (A) shows a moderately high signal intensity corresponding to an area of high attenuation in the left sphenoid. (B) The corresponding T1-weighted MRI with Gadolinium in axial view of the left sphenoid in the same patient showing the moderately high signal intensity centrally corresponding to the eosinophilic mucin. The small polyp shows a different attenuation pattern (black arrow). Peripheral enhancement corresponds to the inflamed mucosa. (C) T2-weighted axial MRI demonstrates central signal void whereas the polyp still can be visualised (white arrow).

that the diagnosis of EFRS should be suspected in any case of CRS regardless of the radiological findings and even in the absence of complete opacification, attenuation or erosion. They imply that clinicians and surgeons should always consider sampling secretions in order to ascertain the possible diagnosis of EFRS. In our experience, the thick inspissated mucin seems to correlate well with the CT images, showing the typical hyperdensities. However, more fluid secretions could also be collected and proven to be eosinophilic mucin upon pathological examination. The latter cases probably reflected the atypical images obtained by the CT scans. This finding does not correlate with the prevailing view of radiologists,[22] which is that there is an evolution from a loose mucus collection into a desiccated mucus plug. In a few patients recurrence was observed in an open and well-aerated cavity before subjective complaints even started. The secretions or casting materials found in the paranasal sinus were thick and tenacious and could hardly been aspirated. This observation suggests a failure of the mucosa to clear the secretions in spite of a large iatrogenic ostium and an obviously well-aerated sinus. The process of entrapment therefore also seems to be caused by the failure of ciliary clearance mechanisms due to the viscosity of the inspissated material, together with the vicious circle of the inflammatory process.

MRI findings

In this series MRI did not play a substantial role in the diagnosis of EFRS. In three cases, some expansion and remodelling was seen. In the other cases some minor bony erosion was the reason for using MRI given the presence of malignancy in the differential diagnosis. It was interesting, however, to observe that the relationship of hyperdensities on CT scan images correlated to a signal void on T2-weighted images in all the cases where eosinophilic mucin was found during surgery (Figures 8 and 9). Further observations are needed to determine whether





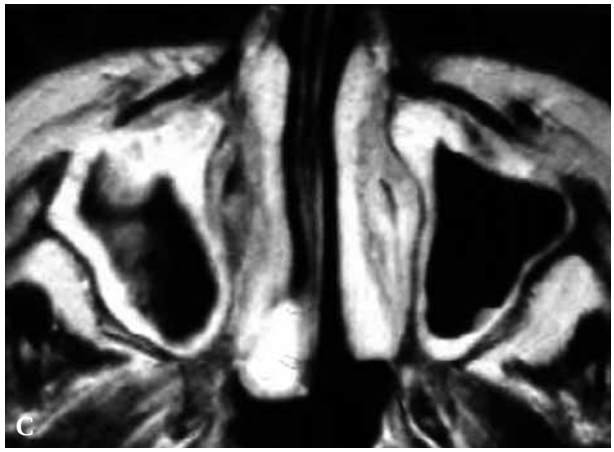


Figure 9
(A) Axial CT scan with soft-tissue window setting showing central hyperdensity in the left maxillary sinus; (B) Axial T1-weighted MRI shows a moderately high signal intensity whereas (C) the axial T2-weighted MRI demonstrates a signal void at the localisation of the eosinophilic mucin.

those features are pathognomonic for this EFRS entity.

Conclusion

EFRS is a distinct clinical entity with non-specific symptoms. In contrast with literature data, EFRS in this series cannot be associated with either young age or allergy. When CT scans show hyperattenuation, they suggest the possibility of EFRS. When CT images with bone window settings are negative, the use of additional CT soft tissue window settings could enable us to find more hyperattenuated regions in the affected sinuses. Even non-specific CT images of CRS should raise the possibility of EFRS. Complete opacification and hyperattenuation are not mandatory. Even aerated sinuses might contain eosinophilic mucin secretions. Additional MRIs were useful in characterising the secretions by showing typical low signal intensity on T1-weighted images and a signal void on T2-weighted images in the EFRS cases. The presence of typical CT and MR signs together seem to be highly predictive and may be pathognomonic for EFRS. More cases are needed to prove this statement.

This study provides clinical support for the findings by Ponikau *et al.*[3] and Braun *et al.*[4] that sampling techniques and histopathology play a primary role in the diagnostic assessment of EFRS.

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Stephan Vlaminck, M.D.
Department of Otorhinolaryngology
St-Jan General Hospital
Ruddershove 10
8000 Bruges, Belgium
Tel.: +32 50 452280
Fax: +32 50 452290
E-mail: stephan.vlaminck@azbrugge.be