The Journal of Laryngology & Otology (2013), ***127***, *867–871*.

doi:10.1017/S0022215113001680

MAIN ARTICLE

Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis: diagnostic criteria

N URI[1], O RONEN[1], T MARSHAK[1], O PARPARA[1], M NASHASHIBI[2], M GRUBER[1]

Departments of [1]Otolaryngology – Head and Neck Surgery, and [2]Pathology, Lady Davis Carmel Medical Center, Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Abstract

Background: Chronic sinusitis is one of the most common otolaryngological diagnoses. Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis can easily be misdiagnosed and treated as chronic sinusitis, causing continuing harm.

Aim: To better identify and characterise these two subgroups of patients, who may suffer from a systemic disease requiring multidisciplinary treatment and prolonged follow up.

Methods: A retrospective, longitudinal study of all patients diagnosed with allergic fungal sinusitis or eosinophilic mucin rhinosinusitis within one otolaryngology department over a 15-year period.

Results: Thirty-four patients were identified, 26 with eosinophilic mucin rhinosinusitis and 8 with allergic fungal sinusitis. Orbital involvement at diagnosis was commoner in allergic fungal sinusitis patients (50 per cent) than eosinophilic mucin rhinosinusitis patients (7.7 per cent; $p < 0.05$). Asthma was diagnosed in 73 per cent of eosinophilic mucin rhinosinusitis patients and 37 per cent of allergic fungal sinusitis patients.

Conclusion: Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis have the same clinical presentation but different clinical courses. The role of fungus and the ability to confirm its presence are still problematic issues, and additional studies are required.

Key words: Sinusitis; Fungus; Eosinophil; Mucin; Diagnosis

Introduction

Rhinosinusitis is defined as an inflammatory process which involves the nasal and paranasal sinuses mucosa. It is estimated that approximately 30 per cent of the US population suffer from rhinosinusitis symptoms, and that the global cost of the disease is over 2 billion US dollars per year.[1]

The commonest cause of acute rhinosinusitis is superimposed viral and bacterial infection. Chronic rhinosinusitis is linked to other aetiological factors such as fungi, allergic reactions, mucociliary disorders, and anatomical and systemic causes.

In recent years, the development of advanced diagnostic methods has facilitated research emphasising the importance of fungal infections in chronic rhinosinusitis. In 1999, Ponikau and colleagues' Mayo Clinic group[2] reported that 96 per cent of 210 chronic rhinosinusitis patients undergoing endoscopic sinus surgery had a positive fungal culture, together with signs of eosinophilic inflammation. Other study groups described differing prevalences of positive fungal cultures, ranging from 0 to 50 per cent.[2,3] These findings support the theory that all types of chronic rhinosinusitis are somehow related to a non-allergic eosinophilic sinus inflammation secondary to fungal infection.[4–6]

Fungal rhinosinusitis is divided into invasive and non-invasive types. The category of invasive fungal sinusitis includes acute invasive (fulminant) fungal sinusitis, chronic invasive fungal sinusitis and granulomatous invasive fungal sinusitis. Non-invasive fungal sinusitis includes fungal ball (mycetoma), allergic fungal sinusitis and eosinophilic mucin rhinosinusitis.

Allergic fungal sinusitis was first described in 1983 as a benign fungal disease of the sinuses in immunocompetent patients.[6] It has been estimated that this disease accounts for 5–10 per cent of all patients with chronic rhinosinusitis.[7] Two-thirds of allergic fungal sinusitis patients suffer from allergic rhinitis, and approximately 90 per cent have increased blood levels of immunoglobulin (Ig) E. Allergic fungal sinusitis is common among adolescents and young adults, and is more common in geographical areas of high humidity. Two-thirds of patients are atopic and half suffer from asthma.[8]

Allergic fungal sinusitis usually has an indolent clinical course but late complications can occur, including proptosis, visual disturbances and facial dysmorphism.

Accepted for publication 3 December 2012 First published online 13 August 2013

There is no clear agreement regarding diagnostic criteria for allergic fungal sinusitis. In 1993, Loury *et al.*[9] suggested criteria which included eosinophilia, elevated IgG or positive skin testing, elevated IgE for fungal antigen, nasal polyps or nasal mucosal oedema, typical computed tomography (CT) or magnetic resonance imaging (MRI) findings, and histological evidence of allergic mucin, fungal hyphae and lack of invasion. In 1994, Cody *et al.*[10] reported the Mayo Clinic experience, and suggested that diagnostic criteria comprise only the presence of allergic mucin and fungal hyphae, or a positive fungal culture. One of the most popular sets of criteria was published by Bent and Kuhn in 1994.[5] It was based upon five elements: IgE-mediated hypersensitivity, polyposis, typical CT scan findings, eosinophilic mucin, and positive fungal culture or staining. Kupferberg and Bent[11] further classified allergic fungal sinusitis into stage 0 (no oedema or allergic mucin), stage I (oedematous mucosa), stage II (polypoid oedema) and stage III (polyps).

In most cases of allergic fungal sinusitis, dematiaceous fungi have been isolated, such as alternaria, bipolaris, curvularia, drechslera, exserohilum and helminthosporium; a small proportion of aspergillus has also been isolated.

Possible findings on CT scan include sinus opacification, bone destruction and thinning of the bony structures secondary to expansion of accumulated mucus. Long-standing disease may present with dramatic radiological findings such as invasion of the skull base and orbit. Calcification within the sinuses is due to the accumulation of elements such as iron and manganese within the mucus.[12]

A suggested radiological staging system was published by Wise *et al.*[13] in 2009, ranking each destroyed bony element or expansile lesion and giving a score of up to 24 points. Although CT scanning is suggested, MRI scanning is an important adjunct when considering dural involvement or intracranial expansion.

Histological staining with haematoxylin and eosin (H&E) highlights mucus and its cellular structures. 'Allergic mucin', also termed eosinophilic mucin by some, comprises over-produced mucus, eosinophils and branching, non-invasive fungal hyphae. Histological analysis shows fragmented eosinophils and Charcot–Leyden crystals, produced by eosinophil breakdown.

Another useful histological staining is Gomori methamine silver, which colours fungi brown-black. Haematoxylin and eosin staining is negative when few fungal hyphae are present; in this case, Gomori methamine silver staining is important as it can delineate fungi when hyphae are sparse.

It should be emphasised that allergic fungal sinusitis does not involve blood vessel or tissue invasion.

During follow up of allergic fungal sinusitis patients, it is useful to monitor blood levels of IgE (specific to the relevant fungal type) as a marker of recurrence.

The mainstays of allergic fungal sinusitis treatment are surgical and medical. The usual surgical treatment is careful endoscopic debridement, followed by a course of systemic corticosteroids. This treatment lowers cytokine levels, which prevents the production, activation and migration of eosinophils. Programmed cell death is also induced. However, there is no published standard treatment protocol. Corticosteroid treatment usually extends for two to three months, including gradual tapering of the dose, but there is currently no consensus regarding corticosteroid dosage or duration.[7,14,15]

Other systemic therapies for allergic fungal sinusitis have been proposed, but none has been clinically proven.

Eosinophilic mucin rhinosinusitis was first described as a subtype of sinusitis which resembled allergic fungal sinusitis clinically and histologically. Eosinophilic mucin rhinosinusitis has been defined as a systemic disease, and therefore bilateral disease is most common. In contrast, patients with allergic fungal sinusitis have an allergic response to fungi, which may occur unilaterally or bilaterally depending on the antigenic stimulation. Eosinophilic mucin rhinosinusitis is significantly associated with asthma, and an increased incidence of aspirin sensitivity has also been reported. Systemic corticosteroid is the treatment of choice for eosinophilic mucin rhinosinusitis. Computed tomography shows similar features to allergic fungal sinusitis (i.e. absence or destruction of the medial nasal wall, hyperattenuation, and thinning of sinus walls), but these are seen bilaterally in most cases. The surgical appearance is of typical mucoid material, with negative fungal cultures.[16]

The present study aimed to compare patients with eosinophilic mucin rhinosinusitis and with allergic fungal sinusitis, followed up in our rhinology clinic, according to certain predetermined clinical criteria. Differences between these two groups have been rarely addressed, and there are few reports describing patients with eosinophilic mucin rhinosinusitis. Clarifying the criteria which differentiate these two patient groups may facilitate quicker and more accurate diagnosis, assisting timely and appropriate treatment.

Materials and methods

We performed a retrospective, longitudinal study including all patients diagnosed with allergic fungal sinusitis or eosinophilic mucin rhinosinusitis in the otolaryngology department of Carmel Medical Center, Haifa, Israel, over a 15-year period (1996–2010).

Thirty-four patients were included in the study cohort: 26 with eosinophilic mucin rhinosinusitis and 8 with allergic fungal sinusitis. All patients were operated upon by the same surgeon.

Allergic fungal sinusitis was diagnosed according to the criteria of Bent and Kuhn, as mentioned above. The diagnosis of eosinophilic mucin rhinosinusitis was based on the presence of extensive, polypoid disease

https://doi.org/10.1017/S0022215113001680 Published online by Cambridge University Press

with thick, eosinophilic mucus and no fungal hyphae, as described in the pathological report. Eosinophilic mucin rhinosinusitis patients were monitored in our rhinology clinic before and after surgery; during this time period, no fungus was identified from various cultures and pathological specimens. Wegener's disease and Churg–Strauss disease were tested for and excluded in all patients.

Information was collected from the following sources, for all patients: demographic data; physical examination and nasal endoscopy; CT scans; pathology reports (all patients had pathological specimens collected during surgery, and all such specimens were reviewed again by the pathologist and the surgeon); bacteriological reports; surgical records; and data on medical treatments, recurrences and follow-up times.

This study was approved by the institutional ethical review board.

Results and analysis

Demographical and clinical parameters were compared, using Fisher's exact test for continuous variables and Student's *t*-test for discrete variables.

Analysis was performed for 26 patients with eosinophilic mucin rhinosinusitis and 8 patients with allergic fungal sinusitis.

Mean age was greater for the eosinophilic mucin rhinosinusitis patients (55.9 years) than the allergic fungal sinusitis patients (34.5 years old) ($p < 0.0001$). Disease was bilateral in 91.6 per cent of eosinophilic mucin rhinosinusitis patients and 62.5 per cent of allergic fungal sinusitis patients ($p < 0.05$). Nasal obstruction was demonstrated in 34.6 per cent of eosinophilic mucin rhinosinusitis patients and 100 per cent of allergic fungal sinusitis patients ($p < 0.05$). Nasal discharge was demonstrated in 57.7 and 37.5 per cent of the eosinophilic mucin rhinosinusitis and allergic fungal sinusitis patients, respectively.

More allergic fungal sinusitis patients (50 per cent) had orbital involvement at diagnosis, compared with eosinophilic mucin rhinosinusitis patients (7.7 per cent; $p < 0.05$). The lamina papyracea was involved by the disease process in 50 per cent of allergic fungal sinusitis patients and 15 per cent of eosinophilic mucin rhinosinusitis patients, a statistically significant difference ($p < 0.05$).

Asthma was diagnosed in 7 per cent of eosinophilic mucin rhinosinusitis patients and 37 per cent of allergic fungal sinusitis patients, although this difference was not statistically significant.

Endoscopic surgery was undertaken for all patients. Some cases were managed with a navigation system to enhance safety, especially when operating upon extensive and destructive lesions (e.g. orbital involvement and frontal sinus surgery).

Most patients needed more than one surgical procedure during the study period; the mean and median number of surgical procedures were respectively 3.3 and 2 for the eosinophilic mucin rhinosinusitis patients, and 1.4 and 1 for the allergic fungal sinusitis patients (the difference between means was not statistically significant).

Histological examination utilised H&E (Figure 1), periodic acid Schiff and Gomori methamine silver stains. Fungi were identified in 87.5 per cent of the allergic fungal sinusitis histological block specimens, and none of the eosinophilic mucin rhinosinusitis specimens.

All patients were available for follow up during the study period. The mean (median) follow-up periods were 9.7 (10 years) for the eosinophilic mucin rhinosinusitis patients and 8 years (8 years) for the allergic fungal sinusitis patients.

Table I summarises results for the two groups.

Discussion

It is important to identify the common elements between the different forms of eosinophilic sinusitis, in order to better define and subclassify this condition. Ferguson[17] reported substantial clinical and immunological differences between allergic fungal sinusitis and eosinophilic mucin rhinosinusitis. Aetiologically,

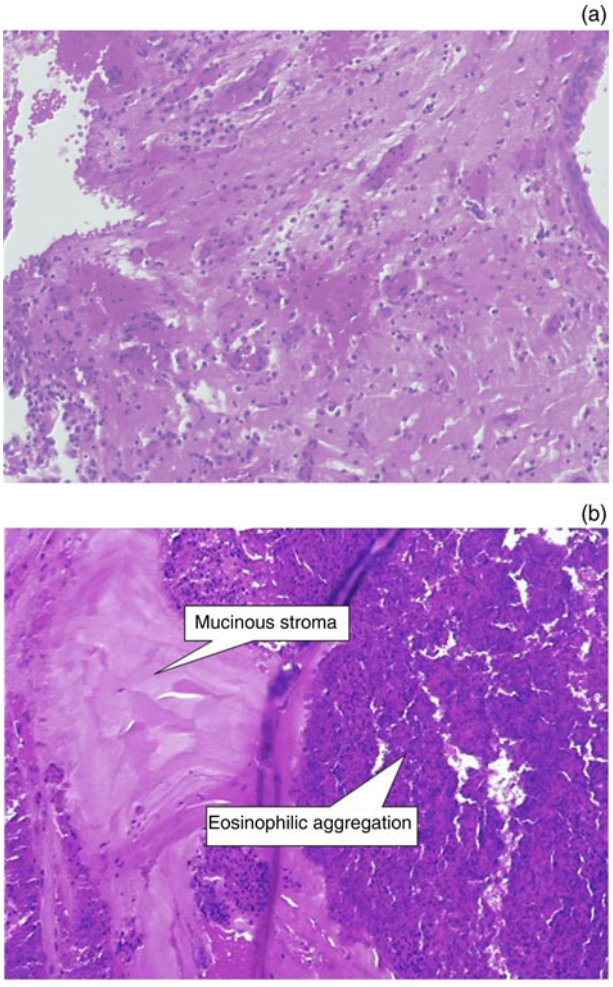

FIG. 1
Photomicrographs showing eosinophilic mucin rhinosinusitis. (H&E; ×20)

https://doi.org/10.1017/S0022215113001680 Published online by Cambridge University Press

TABLE I
PATIENT DATA

Parameter	AFS	EMRS
Total (*n*)	8	26
Age (mean (median); yr)	34.5 (31.5)	55.9 (57.0)
Males (*n* (%))	4 (50)	15 (57.7)
Females (*n* (%))	4 (50)	11 (42.3)
Bilateral disease (*n* (%))	5 (62.5)	25 (96.1)
Orbital involvement (*n* (%))	4 (50)	2 (7.7)
IgE (mean; U/ml)	>500	220.4
Asthma (*n* (%))	3 (37.5)	19 (73.1)
ESS (mean (median, SD); *n*)	1.4 (0.5, 1.7)	3.3 (2, 2.7)

AFS = allergic fungal sinusitis; EMRS = eosinophilic mucin rhinosinusitis; yr = years; Ig = immunoglobulin; ESS = endoscopic sinus surgery; SD = standard deviation

allergic fungal sinusitis is based on the presence of an immunological allergic reaction to fungi in predisposed individuals. This tissue reaction results in the production of allergic mucus rich in eosinophils and non-invasive fungi, together with marked elevation of blood levels of specific IgE antibodies. Ferguson believed that eosinophilic mucin rhinosinusitis represented a local immune reaction occurring secondary to a systemic disorder.[17] In most such cases, IgE levels are within normal limits, with no observed fungi, in contrast to allergic fungal sinusitis patients, who present with elevated IgE due to fungal growth.

According to these basic differences, it is reasonable to divide chronic rhinosinusitis patients into two groups: fungal and non-fungal. The fungal subgroup consists mainly of allergic fungal sinusitis patients. The non-fungal subgroup consists of eosinophilic mucin rhinosinusitis patients and patients with sinusitis and aspirin-sensitive asthma (which deteriorates when treated with non-steroidal anti-inflammatory drugs such as aspirin).

Thick, eosinophilic mucus rich in inflammatory debris is the hallmark of allergic fungal sinusitis. When identified, it is the first clue that the surgeon and pathologist should search for the presence of fungus. But is such fungal presence the defining parameter for subgroup classification?

Another theory proposes that the first stage of disease is the allergic reaction which prompts eosinophilic mucus production, while the second stage is the antigenic reaction to the fungi trapped by this allergic reaction. This theory actually refers to the fungi as a by-product, and known responses to various treatments support this opinion. No anti-fungal treatments have been proven to change the course of the disease. This argument was further reinforced by a 2011 Cochrane database review which concluded that there were no data to support the use of such treatments.[18]

In 2007, Orlandi *et al.*[19] investigated a different perspective concerning the expression of certain genes. They examined DNA from allergic fungal sinusitis patients, eosinophilic mucin rhinosinusitis patients and healthy controls. Four genes were found to be expressed in eosinophilic mucin rhinosinusitis but not in allergic fungal sinusitis, coding for S-100 calcium-binding protein, cathepsin B, sialytransferase 1 and ganglioside activator protein ('GM2'). These genes are responsible for lysosomal activity and act as mediators of inflammatory and tumoural processes. Orlandi *et al.* suggested that the genetic profiles of allergic fungal sinusitis and eosinophilic mucin rhinosinusitis were similar, although differences existed and needed to be further clarified.

Ponikau *et al.*[2] also investigated the role of fungi in chronic sinusitis. In their study, fungus was present in almost all hospital chronic sinusitis patients, as well as in healthy controls. This finding questions the nature of fungi in the aetiology of allergic fungal sinusitis.

Most of the data on the clinical and immunological differences between allergic fungal sinusitis and eosinophilic mucin rhinosinusitis have been derived from Ferguson's 2000 study.[17] This author compared previously published data on 418 allergic fungal sinusitis patients and 40 eosinophilic mucin rhinosinusitis patients, together with information from a further 13 allergic fungal sinusitis patients and 29 eosinophilic mucin rhinosinusitis patients from the author's own database. In the latter database, 41 per cent of allergic fungal sinusitis patients and 93 per cent of eosinophilic mucin rhinosinusitis patients suffered from asthma; in our study cohort, the prevalence of asthma was 37.5 and 75 per cent, respectively. In Ferguson's study, the mean patient age was 30 years in the allergic fungal sinusitis group and 48 years in the eosinophilic mucin rhinosinusitis group; in comparison, our patients' mean ages were 34.5 and 55.9 years, respectively. In Ferguson's own cohort, bilateral disease was present in 55 per cent of allergic fungal sinusitis patients and 100 per cent of eosinophilic mucin rhinosinusitis patients, similar to our own data.

In our cohort, orbital complications were more common among allergic fungal sinusitis patients (50 per cent) than eosinophilic mucin rhinosinusitis patients (8 per cent). These orbital complications presented as diplopia, proptosis and lamina papyracea destruction. This finding suggests a more aggressive behaviour for allergic fungal sinusitis, and justifies special clinical attention for this subgroup of patients.

The number of surgical procedures differed between our two patient groups, with a mean of 1.4 procedures for allergic fungal sinusitis patients but 3.3 procedures for eosinophilic mucin rhinosinusitis patients, although this difference was not statistically significant.

We cannot report accurate data on recurrence among our eosinophilic mucin rhinosinusitis and allergic fungal sinusitis patients. We found that patients who presented with relevant symptoms and signs were first diagnosed with allergic fungal sinusitis; only later, after additional data collection from histological analysis and fungal cultures, was the diagnosis of

https://doi.org/10.1017/S0022215113001680 Published online by Cambridge University Press

eosinophilic mucin rhinosinusitis considered. In some cases, eosinophilic mucin rhinosinusitis was suspected only after multiple surgical procedures and several relapses, and only at that stage did the patient begin to receive appropriate, systemic therapy.

- **Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis are easily misdiagnosed, hindering effective treatment**
- **They have the same initial clinical presentation but different clinical courses**
- **Eosinophilic mucin rhinosinusitis is usually bilateral, and surgical treatment more common**
- **Allergic fungal sinusitis is prone to early orbital involvement**
- **In both, the role of fungi, and diagnostic protocols, are unclear**

Establishing diagnostic criteria to differentiate between allergic fungal sinusitis and eosinophilic mucin rhinosinusitis is difficult. The presence of fungi is essential, and the identification of the culprit is only possible through the use of appropriate stains. It is possible that some of our patients diagnosed with eosinophilic mucin rhinosinusitis actually had allergic fungal sinusitis but that no fungi were identified. We emphasise that the use of Gomori methamine silver staining is essential to the diagnosis: the use of H&E staining alone is inadequate.

Another difficulty in preparing fungal cultures from sinus secretions arises from the differing culture protocols followed by different laboratories. This discrepancy probably explains a significant amount of the observed variance in positive fungal culture rates: various studies have reported rates of between 10 and 97 per cent.

Conclusion

Allergic fungal sinusitis and eosinophilic mucin rhinosinusitis have the same initial clinical presentation, although they are different diseases with (usually) differing clinical courses. Our results indicate higher complication rates and fewer surgical procedures in the allergic fungal sinusitis subgroup, compared with the eosinophilic mucin rhinosinusitis subgroup. More specifically, the clinical course of allergic fungal sinusitis seems to be more aggressive, with a higher prevalence of orbital complications and greater associated morbidity. The role of fungus and the ability to confirm its presence are still problematic issues. Additional studies are required to investigate aetiology, diagnostic standardisation and patient care.

References

1 Lucas JW, Schiller JS, Benson V. Summary health statistics for U.S. adults: National Health Interview Survey, 2001. *Vital Health Stat 10* 2004;**218**:1–134
2 Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA *et al*. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc Sep* 1999;**74**:877–84
3 Corey JP. Allergic fungal sinusitis. *Otolaryngol Clin North Am* 1992;**25**:225–30
4 Millar J, Lamb D. Allergic bronchopulmonary aspergillosis of the maxillary sinuses. *Thorax* 1981;**36**:710
5 Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. *Otolaryngol Head Neck Surg* 1994;**111**:580–8
6 Katzenstein AL, Sale SR, Greenberger PA. Pathologic findings in allergic aspergillus sinusitis. A newly recognized form of sinusitis. *Am J Surg Pathol* 1983;**7**:439–43
7 Schubert MS. Allergic fungal sinusitis: pathophysiology, diagnosis and management. *Med Mycol* 2009;**47**:324–30
8 Manning SC, Holman M. Further evidence for allergic pathophysiology in allergic fungal sinusitis. *Laryngoscope* 1998;**108**:1485–96
9 Loury MC, Leopold DA, Schaefer SD. Allergic aspergillus sinusitis. *Arch Otolaryngol Head Neck Surg* 1993;**119**:1042–3
10 Cody DT 2nd, Neel HB 3rd, Ferreiro JA, Roberts GD. Allergic fungal sinusitis: the Mayo Clinic experience. *Laryngoscope* 1994;**104**:1074–9
11 Kupferberg SB, Bent JP. Allergic fungal sinusitis in the pediatric population. *Arch Otolaryngol Head Neck Surg* 1996;**122**:1381–4
12 de Shazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Swain R, Lyons M *et al*. Criteria for the diagnosis of sinus mycetoma. *J Allergy Clin Immunol* 1997;**99**:475–85
13 Wise SK, Rogers GA, Ghegan MD, Harvey RJ, Delgaudio JM, Schlosser RJ. Radiologic staging system for allergic fungal rhinosinusitis (AFRS). *Otolaryngol Head Neck Surg* 2009;**140**:735–40
14 Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. I. Demographics and diagnosis. *J Allergy Clin Immunol* 1998;**102**:387–94
15 Rupa V, Jacob M, Mathews MS, Seshadri M. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. *Eur Arch Otorhinolaryngol* 2010;**267**:233–8
16 Katzenstein AL, Sale SR, Greenberger PA. Allergic aspergillus sinusitis: a newly recognized form of sinusitis. *J Allergy Clin Immunol* 1983;**72**:89–93
17 Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. *Laryngoscope* 2000;**110**:799–813
18 Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2011;(8):CD008263
19 Orlandi RR, Thibeault SL, Ferguson BJ. Microarray analysis of allergic fungal sinusitis and eosinophilic mucin rhinosinusitis. *Otolaryngol Head Neck Surg* 2007;**136**:707–13

Address for correspondence:
Dr Maayan Gruber,
Department of Otolaryngolgy – Head and Neck Surgery,
Lady Davis Carmel Medical Center,
7 Michal St, Haifa 34362, Israel

E-mail: maayan_gr@yahoo.com

Dr M Gruber takes responsibility for the integrity of the content of the paper
Competing interests: None declared