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Controversies surrounding the categorization of fungal sinusitis

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Though rhinosinusitis is a common disorder, controversies surround the categorization of chronic rhinosinusitis (CRS) and the role of fungus in CRS. The diagnosis of each category is important for optimum therapy and predicting the course. Based on histopathological findings, fungal rhinosinusitis (FRS) can be broadly divided into two categories: the invasive and non-invasive depending on invasion of the mucosal layer. Three types of FRS are tissue-invasive: acute invasive, chronic invasive, & granulomatous. The two non-invasive FRS disorders are fungal ball, and fungus related eosinophilic rhinosinusitis including allergic fungal rhinosinusitis (AFRS). The distinction of granulomatous from chronic invasive type is not beyond controversy as both types have a chronic course and predominant orbital involvement. Maximum confusion surrounds the entity of fungus-related eosinophilic rhinosinusitis, and the definition of AFRS. In the diagnosis of AFRS, the detection of fungi in allergic mucin is considered important, although hyphae are sparse in sinus content. This leads to confusion in definition of this entity, especially with the description of two more closely related entities – eosinophilic fungal rhinosinusitis (EFRS) and eosinophilic mucin rhinosinusitis (EMRS). Recently reports of histologic invasion in possible cases of AFRS were also documented. Currently, there are more questions than answers concerning the categorization of FRS.

Keywords Aspergillus, fungal sinusitis, classification, diagnosis, epidemiology

Introduction

Sinusitis, or more accurately rhinosinusitis, is a common disorder affecting approximately 20% of the population at some time of their lives. It has been estimated to affect approximately 31 million patients (4% of adult population) in the United States each year [1]. It causes significant physical symptoms, severe quality-of-life impairment, and can substantially impair daily functioning. The economic effect is also huge; in the US the direct cost estimated in 1996 at $5.6 billion per year [2]. As the incidence of chronic rhinosinusitis has increased over the last decade, the economic effect is expected to be more. Various causative factors may play a role in chronic rhinosinusitis, including microorganisms, allergic and non-allergic immunological inflammation, and non-infectious, non-immunological causes [3]. In recent years using sensitive methods, positive fungal cultures were reported in more than 90% of patients by some workers, suggesting a major role of fungi in chronic rhinosinusitis [4,5]. Although such a high incidence of fungal rhinosinusitis is debated, it is widely accepted that several types of sinus diseases have been attributed to the presence of fungal organisms in the nasal and sinus cavities. The causes and forms of fungal-related rhinosinusitis are not fully understood and many questions remain unanswered. However, the classification or categorization of fungal rhinosinusitis is important to accurately predict prognosis and choose appropriate therapy.

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Historical perspective on the categorization

The recognition of fungi causing rhinosinusitis was in the 18th century when Plaignaud in 1791 described 'fungus tumour' in the maxillary sinus of a 22-year-old soldier [6]. Oppe first described *Aspergillus* species causing sinusitis in 1897 in a patient with infection of sphenoid sinus. The lesion had extended to the cerebrum through erosion of the bony wall [7]. In 1965 Hora recognized two categories of fungal rhinosinusitis; one non-invasive behaving clinically like chronic bacterial sinusitis, and the other invasive, in which the infection results in a mass that behave like malignant neoplasm, eroding bone and spreading into adjacent tissue, though no histologic evidence of invasion was provided in the report [8]. Subsequently, invasive fungal sinusitis was reported only when histopathologically confirmed true fungal invasion in the tissue [9,10]. McGill *et al*. (1980) reported a third type of fungal sinusitis in immuno-compromised patients: a fulminant form with rapid and malignant course [11]. In 1981, Miller *et al*. and in 1983 Katzenstein *et al*. independently recognized pathophysiologic resemblance between a few cases of chronic rhinosinusitis associated with mucosal plug of sinuses and patients with allergic broncho-pulmonary aspergillosis (ABPA), thus leading to a description of a fourth type, namely allergic *Aspergillus* sinusitis [12,13]. Later it became apparent that melanized fungi are common etiological agents of this allergic type of sinusitis leading to the renaming of this type of fungal rhinosinusitis as allergic fungal sinusitis (AFS) [14–16]. In recent years, the definition of allergic fungal rhinosinusitis has faced its greatest challenge with the demonstration of fungi in eosinophilic mucin independently from Type I hypersensitivity, in most cases of chronic rhinosinusitis [4,5]. Ponikau *et al*. proposed a new term for this condition as Eosinophilic fungal rhinosinusitis to reflect the striking role of eosinophils [4]. In the non-invasive form of fungal sinusitis a new type known as chronic erosive (non-invasive) sinusitis or chronic non-invasive destructive sinusitis was proposed by some workers but was not further substantiated by studies from other centers and remains an enigma [17–19].

In the late 1990s, deShazo *et al*. proposed a new classification of invasive fungal rhinosinusitis based on clinical condition, immune status, histopathology, and fungus isolation: acute (fulminant) invasive, granulomatous invasive, and chronic invasive type [20]. The chronic granulomatous type was first recognized as primary aspergilloma of paranasal sinuses in Sudan by Milosev *et al.* in 1969 [21]. This group of patients was proposed as being different from the chronic invasive type. The chronic granulomatous type is applicable for the presentation of cases from Sudan, India, and Pakistan, where the patients are immunocompetent and are infected almost exclusively with *Aspergillus flavus*. Histopathologically extensive granulomatous response with the presence of fungi within giant cells a common presentation in chronic granulomatous type (Fig. 1a,b). These cases with chronic sinusitis, proptosis and non-caseating granuloma have been distinguished from other chronic invasive fungal sinusitis that has a chronic course, dense accumulation of hyphae resembling fungal ball, and association with orbital apex syndrome, diabetes mellitus and corticosteroid treatment [20].

In the nose and paranasal sinuses, fungi may also persist as visible growth on a mucus crust of an asymptomatic individual and has been described as saprophytic fungal infestation [22]. Considering the above developments in the field of fungal rhinosinusitis, the infection can be broadly divided into two categories; the invasive and non-invasive depending on invasion of mucosal layer. Three types of fungal rhinosinusitis are tissue-invasive: acute invasive (necrotizing, fulminant),

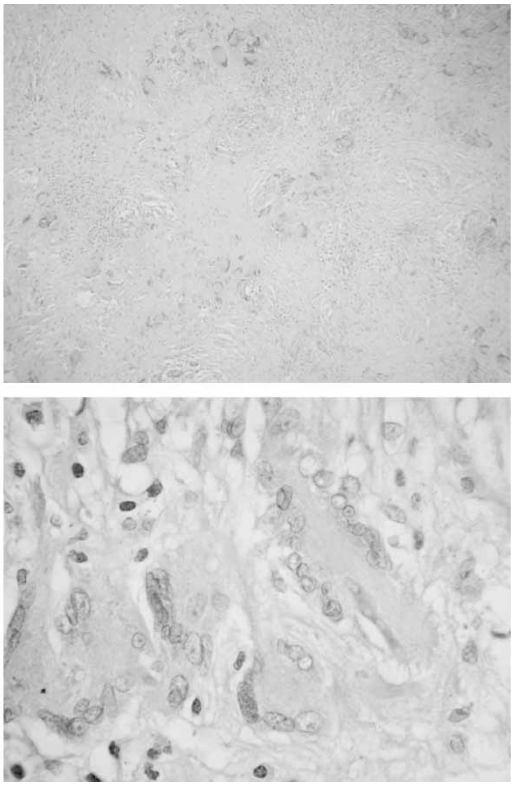

Fig. 1 (a) Photomicrograph showing extensive granulomatous reaction on a fibrotic background. (b) PAS stain showing septate hyphae inside a giant cell.

chronic invasive and granulomatous invasive (indolent). The non-invasive forms may be described in four presentations: saprobic fungal infestation, fungal ball (sinus mycetoma), allergic fungal rhinosinusitis, and eosinophilic fungal rhinosinusitis (Table 1). However, this classification of fungal rhinosinusitis into seven types is not by consensus, therefore remains controversial and is open to discussion. Recently, the American Academy of Otolaryngology Head and Neck Surgery and other related societies through a workshop attempted a consensus of definition, classification of the condition and suggested clinical research strategies for patients with rhinosinusitis [3]. In conclusion, they divided rhinosinusitis into four categories: acute (bacterial) rhinosinusitis, chronic rhinosinusitis (CRS) without polyps, CRS with polyps, and allergic fungal rhinosinusitis. The spectrum of fungal involvement in the CRS was considered from benign colonization to potentially life-threatening invasive disease. Though few important assertions and consensus opinions were made in the disputed areas of fungal rhinosinusitis, the authors recognized the complexity of the situation and emphasized the need for further study.

The need to overcome the controversy

The need to overcome the controversy is especially stressed in the area of optimization of therapy and predicting the prognosis. Without understanding the patho-physiology of the disease, safer and effective treatment cannot be developed. The therapeutic trials are also limited in the area of fungal rhinosinusitis due to lack of widespread acceptance of consensus definition for the different categories of fungal sinusitis. To emphasize the lack of understanding in the area of categorization of fungal rhinosinusitis, different studies from the Postgraduate Institute of Medical Education and Research, Chandigarh, India are compared (Table 2). In our center, with the change in understanding, the prevalence of each type varied over the years [19,23–25]. Though AFRS is seen in 61% cases in the last two years, it is difficult to say categorically that AFRS is emerging as the most common type of fungal rhinosinusitis in North India due to the absence of a consistent definition. Earlier clinicians and histopathologists used to ignore mucus portion of the surgical specimens and tried to look for tissue diagnosis. During the last one and half year after the formation of the working group on fungal sinusitis in our center, included clinicians, mycologists, histopathologists, and radiologists are working in tandem with a better understanding of different categories of fungal sinusitis. However, the prevalence may further vary if the proposed sensitive methods [4,5,26,27] for detection of fungi are employed in the analysis of these cases. Over a period of 16 months, 36 cases of AFRS and 12 patients with eosinophilic mucin rhinosinusitis (EMRS) were reported from the same center and the distinction of the two types was on the presence or absence of fungi on histopathology [28]. Those cases with EMRS might have been diagnosed as AFRS if sensitive methods had been employed. Thus, these varied representations of category of fungal sinusitis over the years from a single center, emphasizes the urgent need to overcome the controversies surrounding categorization of fungal sinusitis.

Controversies

Some of the preferred terms are described in Table 3.

(1) Should we call it fungal sinusitis or fungal rhinosinusitis?

The American Academy of Otolaryngology Head and Neck Surgery and their related societies through their workshop on rhinosinusitis proposed to use the term

Table 1 Classification of fungal rhinosinusitis.

Category	Host immune status	Role of fungus	Course
A. Invasive (invasion of the mucosal layer)			
1. Granulomatous invasive	Immunocompetent	Pathogen	Indolent, chronic
2. Chronic invasive	Often diabetes mellitus, steroid therapy	Pathogen	Chronic
3. Acute invasive	Immunocompromised	Pathogen	Acute
B. Non Invasive (no invasion of mucosal layer)			
1. Saprobic infestation (localized colonization)	Immunocompetent	Saprobe	May consider as early form of fungal ball
2. Fungal ball	Immunocompetent	Saprobe	Chronic
3. Allergic	Atopic	Allergen	Chronic
4. Eosinophilic	majority non-atopic	May take role in deposition of toxic eosinophilic major basic protein [23]	Chronic

Table 2 Category of fungal sinusitis at PGIMER, Chandigarh over the years.

	Study 1 [23]	Study 2 [24,25]	Study 3 [19]	Study 4 (unpublished)
Period (years)	1990–91 (2)	1985–95 (10)	1997–98 (2) (excluding allergic)	2006–07 (1.5)
Number of cases of FRS	50	176	25	105
Categories				
Acute invasive FRS* (%)	2 (4)	12 (7)	–	16 (15)
Chronic invasive FRS (%)	15 (30)	55 (31)	6 (24)	17 (16)
Fungal Ball (%)	31 (62)			
(Classified as non-invasive)	81 (46)	7 (28)	2 (2)	
AFRS** (%)	2 (4)	12 (7)	Not included	64 (61)
Mixed variety (AFRS+CIG)*** (%)	–	–	–	6 (6)
Destructive, non-invasive (%)	Not known	16 (9)	12 (48)	-

*FRS – fungal rhinosinusitis. **AFRS – allergic fungal rhinosinusitis. ***AFRS+CIG – in the same patient simultaneously pathology of allergic fungal rhinosinusitis and chronic invasive granulomatous fungal rhinosinusitis exist.

rhinosinusitis based on the fact that sinusitis is almost always accompanied by concurrent nasal airway inflammation and in many cases, sinusitis is preceded by rhinitis symptoms [3]. However, a fungal ball in paranasal sinuses rarely causes pathology of the nose. In spite of this exception, as most cases of fungal involvement of paranasal sinuses (both invasive and non-invasive) have their concurrent or preceding pathology in nose, the term rhinosinusitis seems more appropriate (Table 3). In allergic fungal sinusitis (AFS) the nasal cavity is also commonly involved and the entity may better be described as an allergic fungal rhinosinusitis (AFRS) though AFS is commonly abbreviated designation.

(2) Is invasive fungal rhinosinusitis properly defined?

Invasive fungal rhinosinusitis was defined with confirmation of sinusitis by radiological imaging and histopathological evidence of hyphal forms within sinus mucosa, sub-mucosa, blood vessels, or bone [29]. The disease was further classified into three varieties: acute fulminant, granulomatous, and chronic invasive.

Acute (fulminant) invasive or acute necrotizing fungal rhinosinusitis is described in the patients with immunocompromised status where histopathology demonstrates hyphal invasion of blood vessels, including carotid arteries and cavernous sinuses; vasculitis with thrombosis, hemorrhage, tissue infarction and acute neutrophilic infiltrates [20]. In some patients the necrotizing reaction may be seen with only minimal inflammation [30]. Plenty of fungi are usually present in that necrotic tissue (Fig. 2). However, the extent and nature of lesion depend on degree of immunosuppression. The term 'fulminant' conveys the rapid destruction and often fatal outcome, which occurs in patients with severe immunosuppression or when untreated. Some of these patients may develop a more protracted form of illness if treatment is started early or with

Table 3 Preferred terms in the categorization of fungal sinusitis.

Preferred terms	Current synonyms	Comments
1. Fungal rhinosinusitis	Fungal sinusitis	As most cases have a preceding or concomitant involvement of nasal cavity
2. Acute invasive fungal rhinosinusitis	Fulminant/ necrotizing fungal sinusitis	As 'necrotizing' lesions are not seen in all patients, and 'fulminant' term conveys rapid destruction and often fatal outcome, which may not be true in all patients
3. Fungal ball	Mycetoma, aspergilloma	As 'mycetoma' signifies specific type of disease with presentation of sinus tract, granuloma (swelling), and grain, which is not present here. Moreover, 'aspergilloma' is not appropriate since it is not always due to *Aspergillus* species.
4. Localized fungal colonization of nasal or paranasal sinus mucosa	Saprophytic infestation	'Infestation' term is used commonly in parasitic infection
5. Eosinophilic mucin	Allergic mucin	As 'eosinophilic mucin' describes the presence of eosinophil or eosinophil degraded product in mucus, which is present in both atopic or non-atopic condition of eosinophil-related fungal rhinosinusitis

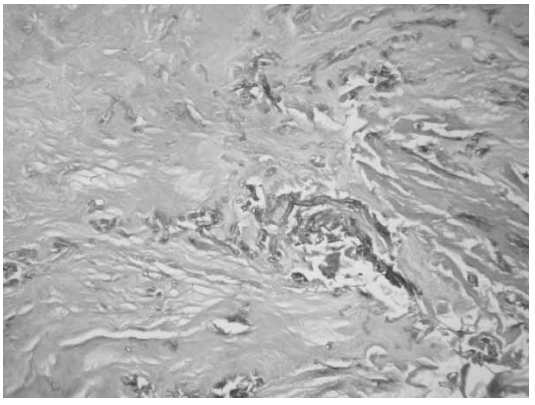

Fig. 2 Photomicrograph showing bland necrosis with numerous aseptate fungal hyphae with no background fibrosis and inflammatory cell reaction.

reversal of immunosuppression [22]. Further, the distinction of acute and chronic nature of the disease depends on host immune status, duration of the illness (more or less than 4 weeks), and vascular invasion. The acute invasive variety is described when immunosuppressed patients develop prominent vascular invasion by hyphae within 4 weeks time course, whereas chronic invasive fungal rhinosinusitis is characterized by minimal vascular invasion and duration over 12 weeks in patients with minimal or no immunosuppression [20,22,29]. Though the duration of illness separates the acute from the chronic variety of the disease, it depends on the aggressive nature of the fungi in the hosts and the host immune status. Treatment may change the pathology from acute invasive stage to chronic invasive or indolent status [22]. Interestingly in one of our patients with acute invasive fungal rhinosinusitis, both necrotizing inflammation and granulomatous foci were seen on histopathology in the same sample (Fig. 3a & 3b). It may cause confusion in categorization of fungal rhinosinusitis. Thus, this distinction requires further clarification.

(3) Are granulomatous invasive and chronic invasive fungal rhinosinusitis separate entities?

The distinction of granulomatous invasive type from chronic invasive type is also not beyond controversy. In granulomatous invasive rhinosinusitis, an enlarging mass is seen in the cheek, orbit, nose and paranasal sinuses in immunocompetent hosts. Proptosis is often a prominent feature. Histopathologically, a granulomatous response is seen with considerable fibrosis. Noncaseating granuloma with foreign body or Langhan's type of giant cells may be seen, sometimes with vasculitis, vascular proliferation and perivascular fibrosis. Hyphae

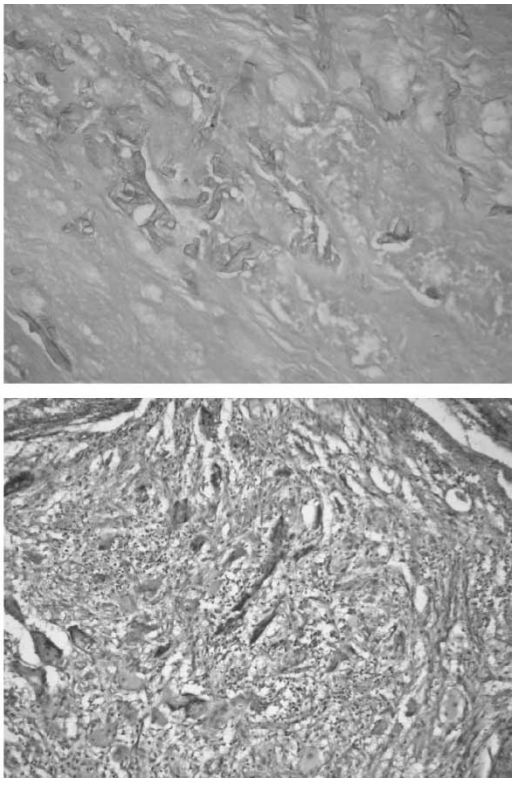

Fig. 3 (a) Photomicrograph showing presence of thin, ribbon-shaped fungal hyphae on a background of bland necrotizing inflammation (acute invasive fungal rhinosinusitis). (b) Focal granulomatous response in some sites in section of tissue from the same patient.

in many occasions are scanty and *Aspergillus flavus* is the primary agent isolated from these cases. The disease primarily has been seen in Sudan, India, Pakistan, and Saudi Arabia [19–21,23–25,31]. In contrast, chronic invasive type is characterized by dense accumulation of hyphae, presence of vascular invasion, sparse inflammatory reaction, *A. fumigatus* isolation and association with orbital apex syndrome, diabetes mellitus and corticosteroid treatment [20,29,32]. The clinicopathological distinctions between these two types are not sharp. Both have a chronic course and prominent orbital involvement. Moreover, no difference in prognosis or therapy is yet apparent based on this distinction. Isolation of different type of *Aspergillus* species may represent separate geographical distribution, and different tissue responses may depend on host immune status. In the geographical region from Sudan to India, it is interesting to observe that *Aspergillus flavus* is the common etiological agent in all types of fungal rhinosinusitis except acute invasive category [19–21,23–25,31]. Diabetics, especially uncontrolled ones, are more susceptible to *Zygomycetes*, which leads to acute invasive

disease instead of chronic invasive course [33]. Some workers even tried to classify granulomatous invasive fungal rhinosinusitis into two types – one that is described in Sudan, other in hypertrophic sinus disease with chronic eosinophilic-lymphocytic granuloma and concomitant AFRS [34,35]. Therefore, all these discussions emphasize the need for further clarification to define different categories of invasive fungal rhinosinusitis.

(4) Is there any localized fungal colonization of nasal mucosa?

Simple colonization of nasal or paranasal sinuses by fungi without any pressure symptoms has been described as saprophytic fungal infestations [22]. The colonization occurs over the mucus crusts often in patients who had a history of previous sinus surgery and is detected upon endoscopic examination. It remains silent until it is detected or presents with foul odor. Previous sinus surgery may disrupt the mucociliary layer and allow the formation of crusts upon which fungi may grow. Further extension of the growth may develop into a fungal ball [22]. The culture examination of the crusts reveal presence of fungi with bacteria admixed with pus [36]. However, as fungi have been detected by culture without any visible growth from the nose of healthy volunteers [4,5], the superficial fungal infestations is differentiated from this condition by the presence of visible growth of fungus within the nasal cavity and not present by culture alone. It is desirable to refer this condition as 'localized fungal colonization of nose and paranasal sinuses' as infestation term is commonly used in parasitic infections (Table 3).

(5) Is it a fungal ball or mycetoma or aspergilloma?

The various terms like mycetoma, aspergilloma, chronic non-invasive granuloma have been described interchangeably in the literature to designate the sinus fungal ball. The disease is defined as the presence of non-invasive accumulation of dense fungal concretion in sinus cavities [36]. The use of the term mycetoma is not technically correct, as mycetoma is chronic local invasion of subcutaneous tissue by bacteria or fungi with the formation of sinus tract, swelling and granule. The term aspergilloma in paranasal sinuses was described in the indolent cases of locally invasive sinusitis, most often from Sudan caused by *A. flavus* [21,31]. Moreover sinus fungal ball is not always caused by *Aspergillus* sp. The term chronic non-invasive granuloma has the problem that histopathological granuloma is not formed in the disease. Therefore, the sinus fungal ball seems to be appropriate term (Table 3) and is defined with the following criteria: radiological evidence of sinus opacification with or without calcification, mucopurulent cheesy or clay like materials within the sinus, a dense conglomeration of hyphae separate from the sinus mucosa, non-specific chronic inflammation of the mucosa, no predominance of eosinophils or granuloma or allergic mucin, no histopathological evidence of fungal invasion of mucosa [37]. However, in a report it was shown that the sinus fungal ball became invasive after the patient received kidney transplant and immunosuppression [38]. In addition, in some patients allergic mucin developed surrounding the fungal ball when steroids were tapered [22,39].

(6) Controversies surrounding eosinophil-related fungal rhinosinusitis including AFRS

Though the existence of allergic disease to fungi in nasal and paranasal sinus cavities was recognized by Miller's group [12] and subsequently Katzenstein's group [13] about three decades ago, controversies remain in defining this group. The term allergic fungal sinusitis (or allergic fungal rhinosinusitis; AFRS) was introduced by Robson *et al*. in 1989 to consider a non-tissue invasive fungal process representing an allergic/hypersensitivity response to the presence of extra-mucosal fungi within the sinus cavity [40], possibly akin to allergic broncho-pulmonary aspergillosis (ABPA) [14]. It is believed that the protein component of the colonizing fungi elicit IgE – mediated allergic mucosal inflammation in the absence of invasion [41]. Moreover, when the sensitized individuals are exposed to an environment of high fungal content, symptoms of airway hyper-responsiveness increase significantly [42]. The fungi deposit within the sinus cavity and elicit a Type I (and possibly Type III) hypersensitivity reaction. This leads to mucosal edema, stasis of secretions, and inflammatory exudates, which eventually obstruct sinus ostia. The process then may expand to involve adjacent sinuses and may produce sinus expansion and bony erosion [43]. Though the presentation of the disease is subtle, occasional dramatic presentations of the disease in the form of acute visual loss, gross facial dysmorphia or complete nasal obstructions were observed [3,15,44]. Why only some patients behave in this acute fashion is not known. Perhaps those patients were oversensitive to fungi, or they had heavy exposure. It is known that the fungi associated with AFRS are diverse, most common being melanized fungi, such as *Bipolaris* species, *Curvularia* species, and *Alternaria* species [15,22,45]. Interestingly, in the Indian scenario *Aspergillus flavus*

was isolated in more than 80% cases of AFRS [23–25,28,46].

As a lot of controversies remained to define AFRS, Bent and Kuhn [16] proposed five diagnostic criteria: type I hypersensitivity, nasal polyposis, characteristic CT scan findings (central areas of hyper-attenuation within sinus cavity on CT scan correspond to areas of hypo-intensity on T1 – weighted MR images, and signal void on T2 weighted MR images), positive fungal stain or culture, allergic mucin with fungal elements and no tissue invasion. Thus, the detection of fungi in allergic mucin is considered important for diagnosis of AFRS besides the other three criteria. However, in a number of patients with AFRS, hyphae are sparse in the sinus content. This led to confusion in the categorization of this entity, especially with the description of two more closely related entities – eosinophilic fungal rhinosinusitis (EFRS), and eosinophilic mucin rhinosinusitis (EMRS) [4,5,47]. Using detection of fungi in nasal lavage as a method of diagnosis, Ponikau *et al*. (1999) demonstrated the presence of fungi in specimens from 96% patients with CRS and did not find Type I hypersensitivity to be prevalent in their study group [4]. They detected fungi in the mucus, which also contained eosinophils and eosinophil degraded products. Sometimes the eosinophils detected in the mucus were in clusters along with few Charcot-Leyden crystals, but mostly they found the eosinophils in the form of cellular debris and crystals. They named the mucin as eosinophilic mucin instead of allergic mucin and coined the term eosinophilic fungal rhinosinusitis (EFRS). These investigators also cultured fungi from nose of 100% of normal volunteers. Braun *et al*. made similar observations using sensitive techniques for detection of fungi [5]. Ponikau *et al*. further progressed their hypothesis by demonstrating toxic major basic protein (MBP) from eosinophil in mucus of the patients with CRS, and found that the level of MBP in mucus remained very high. The toxic level of MBP damages the nasal epithelium from the luminal side. The damaged epithelium might provide an entry port for colonizing bacteria and leads to secondary bacterial infection [27]. However, Ferguson confronted this view by mentioning, 'Eosinophilia or eosinophilic mucin is not synonymous with allergic mucin. Allergies may be associated with eosinophilic mucin, but eosinophilic mucin can be present without evidence of allergies' [22]. Therefore, it appears that AFRS is a distinct entity that requires not only the presence of eosinophilic mucin with hyphae, but also presence of atopy. The question remains whether a separate unrecognized form of non-allergic, fungal eosinophilic inflammation exists that can lead to secondary bacterial infection in a large group of patients with CRS.

Ferguson, in 2000, claimed that eosinophilic mucin could be present and cause rhinosinusitis without the presence of fungi and named the entity as eosinophilic mucin rhinosinusitis (EMRS) [47]. She claimed EMRS is a systemic disease with dysregulation of immunological control. As she found the cases with EMRS were significantly associated with asthma, increased incidence of aspirin sensitivity, and increased incidence of IgG1 deficiency, systemic steroids would be a useful adjunct in those patients. However, she predicted fungal immunotherapy and antifungal agents would be ineffective in patients with EMRS. She proposed four potential mechanisms for EMRS – allergic fungal rhinosinusitis, non-allergic fungal eosinophilic rhinosinusitis, super antigen induced eosinophilic rhinosinusitis, and aspirin exacerbated eosinophilic rhinosinusitis. The distinction between AFRS and EMRS appears important as the therapy differs in these two conditions, but the detection of fungi may become difficult in certain cases with AFRS when fungi are sparse in sinus content. In such situation it is not clear how to distinguish AFRS from EMRS. In a prospective study we found that despite considerable overlap between AFRS and EMRS, type I hypersensitivity, Charcot-Leyden crystals, bony erosion, and heterogeneous opacity and sinus expansion on CT scan were significantly associated with AFRS whereas asthma was significantly associated with EMRS [28]. Taking into consideration all these facts, it can be mentioned that considerable overlap exists between AFRS, EMRS and EFRS in clinical features, radiological and immunological parameters though the difference in therapy in this condition is predicted. In future detailed explorative study for the pathophysiological basis of the difference among these conditions may make our life easy.

In the pathophysiology of AFRS it has been suggested that fungal elements trapped in the mucus in sinus release antigenic material that stimulates IgE, IgG, IgA production [13,48]. What predisposes the condition is not clear. AFRS may entail a pathophysiological course similar to ABPA, with some initial insult causing accumulation of secretions and predisposition of fungal hypersensitivity. It is believed to be a T helper (Th) 2 – like lymphocyte initiated, eosinophil rich inflammatory disease and once initiated, cellular differentiation pathway may lead to the development of an antigen independent permanent phase [34,49]. Numerous models that may be responsible for the pathophysiology of this disorder, including putative role of allergens, fungal derived antigens, bacteria and

bacterial derived superantigens are postulated [49]. A role has been proposed for IgE specific staphylococcal derived superantigens in the pathogenesis of CRS associated with nasal polyps. Analysis of specific IgE revealed presence of IgE antibodies to *Staphylococcus aureus* enterotoxins in about 60% patients with nasal polyp, and 80% patients with nasal polyp and asthma [50]. All these studies indicate that until there is definite evidence that T-cells within the sinuses are actively responding to fungal antigens and further demonstration that removal of fungal antigens ameliorates the disease, the case against fungus remains circumstantial only. Fungus may be a bystander in the whole process.

The controversy regarding the definition of AFRS is further intensified with the well-documented reports of histologic invasion in possible cases of AFRS [34,51]. Thakar *et al*. claimed that the lack of similar invasive histopathological features in other reports of AFRS may possibly relate to pathological sample errors [51]. Foci of granulomatous inflammation in patients of AFRS with orbital apex involvement have also been reported [52]. In our unpublished series of 105 patients (Table 2), six patients had simultaneous granulomatous lesions and histopathologic features of AFRS (Fig. 4a–d). After the documentation of possible histological invasion in AFRS cases, discrete compartmentalization of fungal sinusitis into invasive and non-invasive forms seems debatable. Some workers support the view that different types of fungal sinusitis represent a progressive spectrum of the disease with initial colonization to semi invasive or invasive forms [53,54]. Such a progression may be precipitated by a change of host defenses [38].

Extending the hypersensitivity process in the causation of AFRS, some workers claimed the consistent presence of AFRS and ABPA in the same patients and termed the process as Sino-bronchial Allergic Mycosis (SAM Syndrome) [55]. It is not clear whether it should be considered as a separate entity as all AFRS patients do not have simultaneous ABPA.

(7) Is there any entity of non-invasive destructive fungal rhinosinusitis?

Rowe-Jones and Moore-Gillon in 1994 proposed chronic destructive but non-invasive (semi-invasive) form of fungal rhinosinusitis [17]. It is categorized by sinus expansion and bony erosion, but with no histologic evidence of tissue invasion. In this state, the pathogens lead to progressive, chronic inflammation,

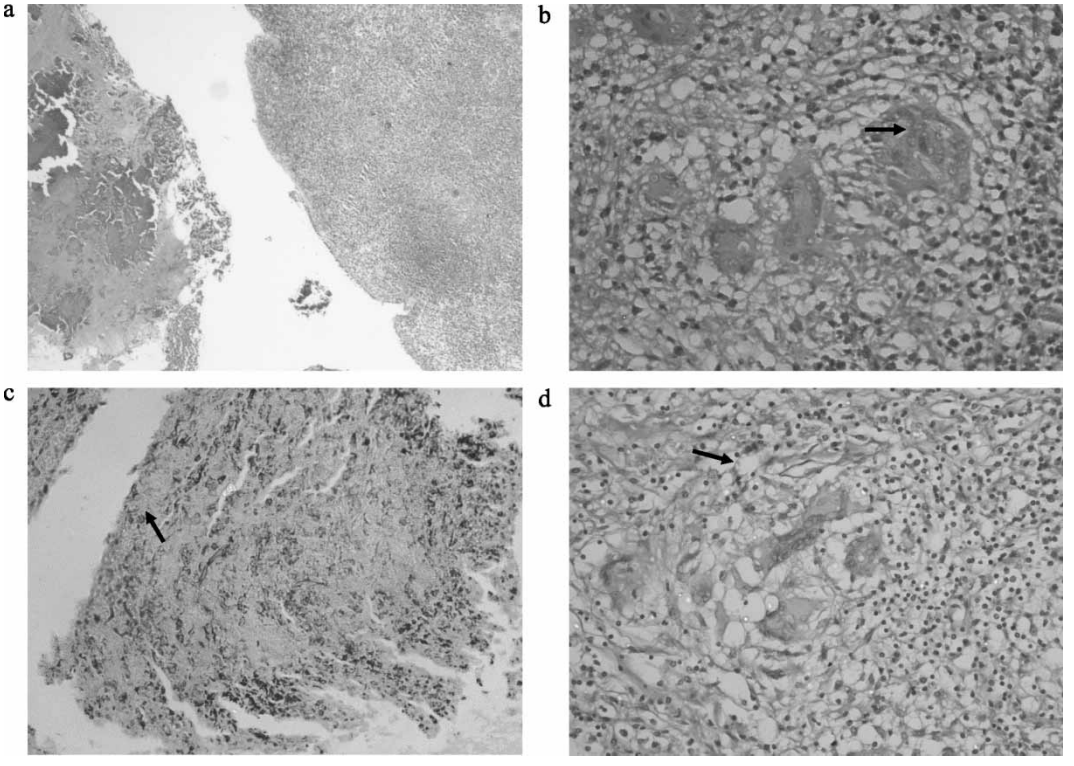

Fig. 4 Photomicrograph showing (a) a combination of allergic mucin and granulomatous response, (b) a cluster of giant cells with unstained fungal hyphae in one of them, (c) septate fungal hyphae on Grocott methenamine silver stain; and (d) septate fungal hyphae in one of the giant cells on PAS stain.

intermediate between allergic, sinus fungal ball, and chronic invasive state. Even though inflammation and bony erosion were evident, these cases had not progressed to produce facial mass or proptosis associated with invasive disease. Such example of semi-invasive pulmonary aspergillosis also exists [56]. However, this entity may be a variant of non-invasive types in which the fungal mass destroys the sinus wall by pressure [57]. In characterizing chronic non-invasive fungal rhinosinusitis, all authors refer to fungal ball or AFRS. However, the difference between this entity and fungal ball, the group proposed that their clinical course was more violent than fungal ball; they required more extensive endoscopic operation and longer follow up. The similarity between destructive non-invasive fungal rhinosinusitis and AFRS was the long course of the disease, the erosive appearance in CT scan, the need for extensive endoscopic surgery, and the long follow up period. The differences between the two groups were the different pathological appearance, immune status and treatment. The existence of this separate entity and treatment protocol are still to be settled [18]. At least in our experience, we re-diagnosed most of our earlier cases with non-invasive, destructive types as AFRS after careful histopathological examination (unpublished observation).

Conclusion

The above discussion emphasizes the fact that fungal rhinosinusitis is still a complex process and understanding of the disease especially pathophysiology is limited. The purpose of clear differentiation and definition of categories of fungal rhinosinusitis is related to the development of a management protocol of each category. A prospective systematic study involving clinicians, microbiologists, pathologists, radiologists, and immunologists as a team and simultaneous discussion among the scientists in different centers in the form of working group may resolve the controversies. The International Society for Human and Animal Mycology has taken an important step by formation of a working group on 'Fungal sinusitis'. The success of this effort depends on participation of interested scientists across the globe. The effort of the American Academy of Otolaryngology Head and Neck Surgery and other related Societies is commendable, as they at least resolved some of the confusion by consensus opinion.

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