

The role of fungi in the airway of chronic rhinosinusitis patients

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Purpose of review

To analyze the role of fungi in the upper and lower airway in chronic rhinosinusitis patients.

Recent findings

Recently, the involvement of the lower airway (as asthma, small airway disease and bronchial hyperresponsiveness) in chronic rhinosinusitis patients had been documented. Fungal spores after inhalation are submerged in the aqueous lining layers of the airway. The site depends on the size of the inhaled spores. The process of inhalation, retention and clearance of fungal spores may explain the positive culture results in both normal subjects and in most chronic rhinosinusitis patients. Fungal culture of different parts of the upper and lower airway in chronic rhinosinusitis patients had no correlation with cellular changes (local eosinophilia) and other clinical parameters. In chronic rhinosinusitis, with persistence of the chronic inflammatory process, the cells may be activated nonspecifically.

Summary

The role played by fungi in most chronic rhinosinusitis patients as the target antigen of initiation of such chronic inflammation is still debated. With the presence of chronic eosinophilic inflammation in chronic rhinosinusitis, an exaggerated reaction to various inhaled antigens is anticipated. The role of fungi will be confirmed only when T cells within the sinuses are shown to be actively responding to fungal antigens cultured from the sinus and with the demonstration that their elimination will stop the disease.

Keywords

airway, asthma, chronic rhinosinusitis, fungi

Introduction

Chronic rhinosinusitis (CRS) is one of the most common long-term illnesses in the world. It affects approximately 15% of the adult population in western countries [1]. The disorder has also been demonstrated to cause significant physical symptoms that negatively affect quality of life [2]. In addition, CRS is also a significant health problem that results in a large financial burden on societies [3]. When associated with other comorbidities such as lower airway diseases, an increased burden on the individual and community levels is anticipated [4].

The etiology of CRS with or without nasal polyps is debated and its pathophysiology remains controversial. Theories advanced over the years include ostiomeatal complex changes, allergy, infection and inflammation. The vain hope is that a universal theory of causation will be produced.

Conflicting reports came with the role of fungi in the etiology of CRS [5,6]. The presence of fungi is a prerequisite to prove such a causal relationship between moulds and CRS. Also, the identification of these fungi is crucial for the diagnosis and treatment of such a new disease entity termed eosinophilic fungal rhinosinusitis, which is claimed to affect all CRS patients [5].

The presence of fungi due to a disturbance in the process of inhalation, retention and clearance of fungal spores that begins as soon as the spores make contact with the airway must be differentiated from fungal-related diseases of the paranasal sinuses.

Thus, the present review analyzes the role of fungi in different parts of the airway in CRS patients.

Classification and clinical definition of chronic rhinosinusitis

Rhinosinusitis can be defined as any inflammation of the nasal and paranasal sinus mucosa that results in signs and symptoms. Most classifications systems of rhinosinusitis, however, were based on the duration of symptoms and/or the specific sinus involved.

In 1997, the International Rhinosinusitis Advisory Board [7] published the clinical classification of rhinosinusitis in adults. The clinical symptoms and signs were divided into major and minor criteria. To be defined as CRS, symptoms of rhinosinusitis had to be present for 12 or more weeks, and patients had to have a combination of

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Abbreviations

ABPA allergic bronchopulmonary aspergillosis
AFS allergic fungal sinusitis
BAL bronchoalveolar lavage
CRS chronic rhinosinusitis
PCR polymerase chain reaction

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two or more major factors or one major factor and two minor factors [7].

A more recent European position paper on rhinosinusitis and nasal polyps endorsed these criteria, but also recommended confirmation by nasal endoscopy or computed tomography scan. Endoscopic signs include the presence of polyps, mucopurulent discharge from the middle meatus or edematous and mucosal obstruction primarily in the middle meatus. The computed tomography changes are mucosal swelling or fluid levels within the ostiomeatal complex or sinuses. According to the European position paper, the severity of sinus disease can be scored using a visual analogue scale for the symptoms and endoscopic or computed tomography scores for the clinical findings [8].

Relationship between chronic rhinosinusitis and the lower airway

The link between the upper and lower airway is now well established, and has led to the concept of the united airway. The relationship between CRS and the lower airway may be demonstrated by several means. They may be related on an epidemiological basis. Also, demonstration of improvement in the lower airway after medical or surgical treatment of rhinosinusitis can support such affiliation. Recently, 60% of CRS patients were shown to have associated lower airway involvement [4]. Asthma, which is a complex clinical syndrome characterized by a variable lower airflow obstruction together with lower airway inflammation and bronchial hyperresponsiveness, was observed in 24%. Another two hidden lower airway involvements were observed: small airway disease and bronchial hyperresponsiveness. Small airway disease with involvement of small bronchioles less than 2–3 mm in internal diameter was observed in 36%. Bronchial hyperresponsiveness, which is a functional disorder reflecting the potential of variable airway obstruction, was observed in asthma and in 33% of small airway disease patients [4]. Another study demonstrated computed tomography scan abnormalities in about 84% of the severely asthmatic patients and extensive sinus disease was seen in 24% of those patients [9].

Classification and forms of fungal rhinosinusitis

Five forms of fungal rhinosinusitis disorders are currently recognized (Table 1), as clarified by deShazo *et al.* [10]. Specific histopathological criteria are now applied to help

Table 1 Forms of fungal rhinosinusitis

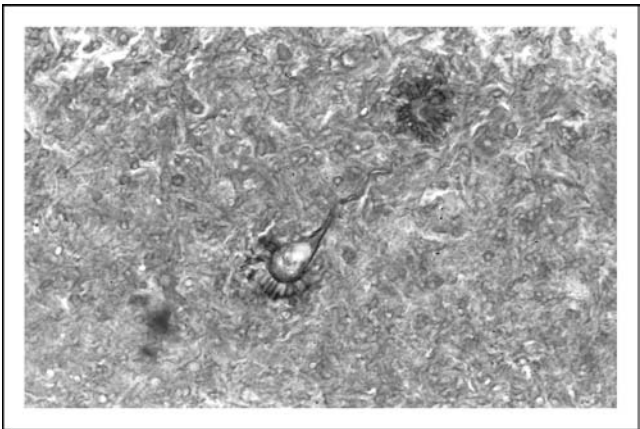
Invasive fungal rhinosinusitis
Acute invasive fungal rhinosinusitis
Chronic invasive fungal rhinosinusitis
Granulomatous invasive fungal rhinosinusitis
Noninvasive fungal rhinosinusitis
Fungal ball
Allergic fungal rhinosinusitis

differentiate the various forms of fungal rhinosinusitis, which have different clinical characteristics, treatment and prognosis [11].

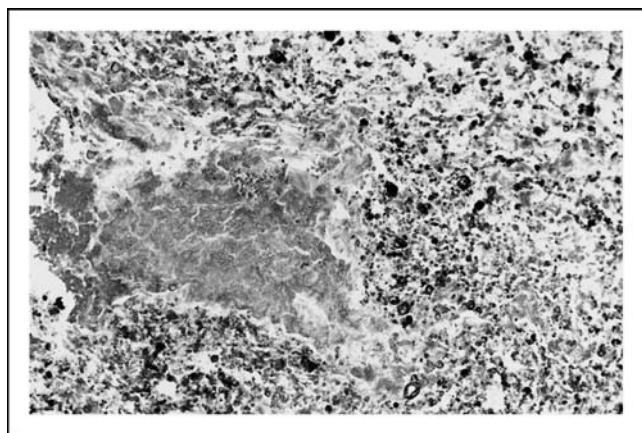
Three of the disorders are tissue-invasive, whereas the other two are not tissue-invasive. Invasive disease of the sinuses is rare and almost exclusively seen in immunocompromised patients, related to either underlying predisposing conditions like diabetes or iatrogenic immunosuppression as in transplanted patients [10]. The diagnosis of the invasive form is not mistakable, whereas the main discussions are around the noninvasive forms (the topic of our study).

Fungal balls represent a noninvasive form of fungal rhinosinusitis, showing an accumulation of many fungal hyphae compressed into a mat or ball lying within the sinus lumen extrinsic to the mucosa [12]. The incidence of fungal balls has been estimated at 3.7% of all inflammatory sinusitis cases going to surgery [13]. Only one sinus is usually involved. Limitations of fungal balls to certain sinuses can be explained because of the lack of viability and sporulation of the fungi (Fig. 1) together with possible sinus ostium occlusion [14**]. Failure of the fungi (from the fungal ball itself) to grow on fungal culture is common, with fungal culture rates of 23 [13] and 50% [10]. This can enlighten the weak nature of the common ubiquitous identified fungi when present in the paranasal sinuses to cause fungal balls in immunocompetent individuals. The fungi reported to cause fungal balls include *Aspergillus fumigatus*, *Aspergillus flavus*, *Alternaria* sp., *Rhizopus microsporus* and *Pseudallescheria boydii* (Fig. 2) [14**]. Also, because of the absence of chronic inflammation that can upload the fungal existence to allergic fungal sinusitis (AFS), most cases of fungal balls did not change to AFS or eosinophilic fungal rhinosinusitis with such prolonged exposure to such fungi!

Figure 1 Spore formation in fungal balls



Limitations of fungal balls to certain sinuses can be explained because of the lack of viability and sporulation of the fungi.

Figure 2 Types of fungi in fungal balls

The fungi reported to cause fungal balls include *Aspergillus fumigatus*, *Aspergillus flavus*, *Alternaria* sp., *Rhizopus microsporus* and *Pseudallescheria boydii*.

First reported in 1981 by Miller *et al.* [15], AFS is a noninvasive fungal rhinosinusitis with associated hyperplastic eosinophilic sinusitis that represents an allergic and immunological response to the presence of fungal hyphae found within the sinus cavities. The constellation of clinical, radiographic and immunologic features helped to define the disease, and these features have been the focus of a number of diagnostic criteria [16,17]. Patients with AFS uniformly demonstrated five characteristics: gross production of eosinophilic mucin-containing non-invasive fungal hyphae, nasal polyposis, characteristic radiographic findings, immunocompetence and allergy to fungi [17]. Several diagnostic criteria for AFS are primarily histopathological and obtained from sinus surgery specimens (Table 2) [18].

In 1999, a hypothesis of CRS was proposed by Ponikau *et al.* [5] that suggested colonizing fungi in sinus mucus play a much broader role in the pathogenesis of CRS. By using a sensitive culture technique, 93% of 101 consecutive patients with CRS demonstrated positive fungal cultures from nasal lavage. Limiting the diagnostic criteria to the presence of fungi and the presence of allergic mucus-containing clusters of eosinophils, new questionable criteria (applicable to all CRS patient) were suggested.

Table 2 Histopathological diagnostic criteria for allergic fungal sinusitis (all criteria must be met) [adapted from [18]]

1. Characteristic allergic mucin is seen histopathologically and/or grossly
2. Fungal stain is positive for hyphae within the allergic mucin, but not in the mucosa, or the surgical sinus fungal culture is positive in an otherwise characteristic patient
3. The sinus mucosa demonstrates eosinophilic-lymphocytic inflammation without evidence for tissue necrosis, granulomas or fungal invasion
4. Other fungal diseases are excluded

Fungal culture in chronic rhinosinusitis

Previously, the presence of fungi in the mucus of the nasal cavity or paranasal sinuses was a required criterion to diagnose AFS [17,19]. Nevertheless, to prove the presence of fungi has been difficult – several detection methods and culture techniques have been used for many years, resulting in varying rates of fungal detection [20,21].

To improve the sensitivity of fungal culture techniques, in addition to the adequate amount of mucus that needs to be harvested, rapid transportation and processing in specialized mycological laboratory is a prerequisite. Under laminar flow to prevent contamination, using mucolytic agents allowed the disulfide bridges to be chemically broken in the mucin to release the entrapped fungi. This procedure liquefied the mucus and allowed direct contact of the fungi with the culture media [5]. Increasing the number and type of fungal culture media used increases the number and range of fungal isolates [22]. Also, culturing at different incubator temperatures (25, 30, 32 and 37°C) can allow more fungal yield.

Fungi in CRS patients are found mainly in sites where mucus is present. Recently, striking progress has been made in the development of better techniques to detect fungi in nasal secretions. The technique chosen as a method to sample the nose is important with respect to the expected yield. Using the irrigation techniques allows sampling of a large amount of mucus in comparison to swab or brush techniques according to the sampled area. This can be seen clearly in Jiang *et al.*'s [23] study, with a higher culture rate in lavage specimens (49%) as compared to middle meatus swab specimens (11.8%).

Employing nasal lavage allows us to reach areas of the nasal mucosa exposed to the respiratory airway as well as the main nasal mucus transport pathway originating in the paranasal sinuses. The drawback of the irrigation technique is that it likely samples the nasopharynx, nasal vestibule and perhaps the skin of the face. All the areas must be kept in mind when explaining nasal lavage culture studies.

Several authors (Table 3) [5,6] used the same method of collection with a high fungal yield in CRS patients (96 [5] and 91.3% [6]) and nearly the same results were observed in the normal control.

In our recent study validating our mycological culturing technique using the same technique of collection as Ponikau *et al.* [5], the authors found a 100% culture rate from the total nasal lavages of healthy subjects [14**]. Using irrigation suction for specific areas in a sequential order under endoscopic guidance, nearly the same total culture rate was observed in CRS patients (nasal

Table 3 Review of fungal studies

Study	CRS patients							Normal control			
	Collection site	Method	Culture result (%)	<i>Aspergillus</i> (%)	<i>Alternaria</i> (%)	<i>Cladosporium</i> (%)	<i>Penicillium</i> (%)	Others (%)	Collection site	Method	Culture result (%)
Ponikau <i>et al.</i> 1999 USA [5]	Nasal lavage	Culture	96	29.6	44	39	43		Nasal lavage	Culture	100
Braun <i>et al.</i> 2003 Austria [6]	Nasal lavage	Culture	87	83.3	22.9	41.4	56.6		Nasal lavage	Culture	91.3
Ragab <i>et al.</i> 2006 Belgium [14**]	Nasal cavity lavage		36	24	4	16	16		Nasal lavage	Culture	100
	Middle meatus lavage		44	28	0	0	12				
	Nasal vestibule		8	4	0	0	0				
Jiang <i>et al.</i> 2005 China [23]	Nasal lavage	Culture	49								
	Middle meatus swab	Culture	11.8								
Polzehl <i>et al.</i> 2005 Germany [24]	Nasal lavage	Culture	25	25.9			3.7				
	Nasal lavage	Polymerase chain reaction	44	42			26.3	Pan-fungal antigen 63			
Kim <i>et al.</i> 2005 Korea [25]	Nasal lavage	Culture	23.2	3.7		2.4	4.9	<i>Candida albicans</i> 12	Nasal lavage	Culture	30
	Nasal lavage	Polymerase chain reaction	92	34.4			9.8	Pan-fungal antigen 92	Nasal lavage	Polymerase chain reaction	97.5
Scheuller <i>et al.</i> 2004 USA [26]	Middle meatus brushing	Quantitative polymerase chain reaction	21						Middle meatus brushing	Quantitative polymerase chain reaction	37
Murr <i>et al.</i> 2006 USA [27]	Middle meatus brushing	Quantitative polymerase chain reaction	45						Middle meatus brushing	Quantitative polymerase chain reaction	45.9
Kostamo <i>et al.</i> 2004 Finland [28]	Sinus mucus samples	Culture	21						Nasal lavage	Culture	
Gosepath <i>et al.</i> 2004 Germany [29]	Surgical polyp specimens	Polymerase chain reaction	100		100			Pan-fungal antigen 100	Healthy tissue	Polymerase chain reaction	66
Rao <i>et al.</i> 2006 USA [30]	Mucosa of the middle meatus	Polymerase chain reaction	6.5						Mucosa of the middle meatus	Polymerase chain reaction	29
Catten <i>et al.</i> 2001 USA [31]	Nasal brushing	Polymerase chain reaction	42						Nasal brushing	Polymerase chain reaction	40

vestibule 8%, middle meatus lavage 44% and nasal cavity lavage 36%) [14^{••}]. All the above results can explain the sensitivity of the used culture technique.

Other studies revealed lower culture rates using the same nasal lavage technique in CRS patients (23 [24] and 23.2% [25]). In fungal culture, the presence of at least one viable spore per specimen is theoretically sufficient for a positive result. Nonviable fungus material, however, is generally not detected by culture techniques. It can be detected using other techniques, e.g. polymerase chain reaction (PCR). In comparison to their lower fungal culture yield, using the PCR both Polzehl *et al.* [24] and Kim *et al.* [25] (Table 3) revealed a higher fungal detection rate (44 and 92%, respectively). The time lapse between specimen collection and culture can explain the lower culture rate and the difference between fungal culture and PCR results.

Middle meatal cultures correlated highly with antral punctures and appear to be an effective noninvasive diagnostic tool for diagnosis of the microbiology of CRS [31,32]. In our [14^{••}] study, the middle meatal endoscopic-guided culture was used with a positive fungal culture rate of 44%. The more limited lavage of a well-determined site without contamination from other areas explains the difference between that study and the other studies using nasal lavage techniques. Scheuller *et al.* [26] and Murr *et al.* [27] (Table 3) used another sampling technique by scraping the nasal mucosa of the middle meatus with a cytology brush. Using PCR, they reported fungal DNA elements in 21.1 and 45%, respectively, of the middle meatus of CRS patients and also in the normal control.

Aspergillus, *Pencillium* and *Cladosporium* were the most common cultured fungi in our study [14^{••}]. This corresponds well with the types of fungal biodiversity in Belgium homes (where the study was done) as studied by Noland *et al.* [33]. Also in Europe, Braun *et al.* [6] had a higher culture rate of the same genera (*Aspergillus* 83.8%, *Pencillium* 56.6% and *Cladosporium* 41.4%) and lower rate of *Alternaria* (22.9%). In Ponikau's study [5] that was conducted in the USA, a higher culture rate for *Alternaria* was found (44%) than the other genera (*Aspergillus* 29.6%, *Pencillium* 43% and *Cladosporium* 39%) (Table 3). Other studies identified little or no *Alternaria* [25,28]. In other areas of the world, e.g. Asia, *Candida* is the most common cultured fungi [23,25]. Granville *et al.* [34], using histological correlation of fungal sinusitis to culture, identified that fungal culture in classic AFS was mostly *Dematiaceous* fungi. Reviewing the literature, the most common identified fungi in AFS were *Dematiaceous* (87%) and *Aspergillus* (13%) [35]. The lower rate of culture of *Dematiaceous* and the higher culture rate of other genera in CRS studies can clarify the erroneous diagnosis of eosinophilic fungal rhinosinusitis for all CRS patients.

Fungi are ubiquitous saprophytes that reproduce by the formation of spores that are able to enter the respiratory tract by means of inhalation [36]. The retention and clearance of fungal spores after inhalation depends on many factors, including physical and chemical properties of both the spores and the mucous surfaces, anatomic location of the deposition site, and the nature of the structures with which the particles interact at the site of deposition (type of mucociliary layer at the air–fluid interface, the aqueous phase, free cells, epithelial cells or dendritic cells residing near the basal aspect of epithelium) [36]. Geiser *et al.* [36] found in his experimental study that fungal spores after inhalation are submerged in the aqueous lining layers of the airways. Thus, during respiration many spores will stick more to the mucus gel layer than to the skin of the vestibule that contains long-chain fatty acids that inhibit fungal colonization [37]. This was shown by the authors with a higher fungal culture rate from the nasal cavity (36%) and bronchoalveolar lavage (BAL) (28%) compared to the nasal vestibule (8%) [14^{••}]. Also, as the nose represents the first mucus-lined station of the respiratory tract, more fungi were recovered from the nasal lining than from the lower airway [14^{••}].

The immune response to fungi in chronic rhinosinusitis

The normal immune response varies with respect to the fungal species encountered. The relative importance of specific innate and adaptive defense mechanisms differs depending upon the organism and anatomical site of interaction. Within a species, the fungal morphotype (e.g. yeast, pseudohyphae and hyphae of *Candida albicans*) may be an important determinant of the host response. Whereas yeasts and spores are often effectively phagocytosed, the larger size of hyphae precludes effective ingestion and requires interactions of different inflammatory cells [38]. Several shared defense mechanisms are operative in response to a range of fungi. Neutrophils, eosinophils, macrophages and monocytes are fundamentally important antifungal effectors cells.

In recent studies data have been generated showing that patients with CRS have peripheral blood T cells that proliferate and produce interleukin-5 in response to *Alternaria* [39], although it was found with a varying limited range (0–44%) in cultures of CRS patients. Circulating T helper 2-like cells could reflect the prevalence of *Alternaria* in the subject's environment, and the secondary development of antigen-presenting process and immune responses. This antigen-presenting process via the dendritic cells was clarified in the Gosepath study [29] with identification of fungal DNA in all polypoid tissue, mostly of *Alternaria*. These data [39] need to be compared with those derived from healthy nonallergic, nonasthmatic controls, as well as controls with allergic rhinitis and asthma.

Circulating *Alternaria*-specific T cells may be a relatively common and nonspecific development in allergic rhinitis, asthma and eosinophilic sinusitis.

Sensitization to *Alternaria* was previously shown to be common and is a risk factor for the development of asthma [40,41], and hypersensitivity to this fungus in asthma and eosinophilic CRS may reflect the ubiquitous nature of *Alternaria* and the presence of a robust T helper 2-like lymphocyte-mediated disease. With the proliferation of mature dendritic cells in the airways, immune responses to bystander allergens (such as those derived from *Alternaria*) are likely to develop and do not necessarily suggest that such immune responses are responsible for disease diathesis [42•]. Pant *et al.* [43] studied the fungal-specific humoral response in eosinophilic CRS. In contrast to IgE, fungal-specific IgG, IgM and IgA were present in the serum of all eosinophilic CRS patients and controls, consistent with mucosal exposure to common environmental fungi. Destruction of fungal hyphae may merely represent a nonspecific feature of the activated primed eosinophils. It is equally reasonable that any 'primed' eosinophils (e.g. Churg–Strauss vasculitis, asthma or idiopathic hypereosinophil syndrome) could function equally well in a fungicidal pattern. Eosinophils lack antigen receptors. Therefore, their ability to destroy fungal hyphae represents a nonspecific innate immune response or opsonization of the fungus – in the absence of IgE – by IgG (or IgA) as was demonstrated in Pant *et al.* [43] study.

Polypoid and nonpolypoid CRS (CRSwNP vs. CRSsNP) generally shows different patterns in cellular content and gross histological changes within the tissue, especially edema and fibrosis formation. In the sinus fluid of patients with CRSsNP undergoing surgery, inflammatory cells are predominantly neutrophils, as is observed in acute sinusitis, but a low percentage of eosinophils, mast cells and basophiles might also be found [44,45]. In a recent study evaluating the percentage of eosinophils (of 1000 inflammatory cells counted per vision field), 31 patients with untreated chronic sinusitis without neutrophils all had less than 10% eosinophils (overall mean, 2%), whereas in specimens from 123 untreated patients with neutrophils, 108 samples showed more than 10% eosinophils (overall mean 50%) [46]. Among the inflammatory cells, activated eosinophils are a prominent and characteristic feature in about 80% of patients with CRSwNP [46].

The histological markers for AFS are the striking numbers of tissue eosinophils in the sinuses in contrast to an absence of eosinophils in the sinuses of healthy controls [47,48]. Khan *et al.* [49] also showed the presence of numerous intact or degenerated eosinophils (eosinophils concretion) in the sinus contents (mucin) of AFS. In our

[14••] study, eosinophilia was identified in only 33.6% of the positive fungal middle meatal culture cases. Watanabe *et al.* [50], in a transmission electron microscopic study of the nasal discharge from five patients with AFS, showed that fungal hyphae surrounded by eosinophils were observed in only one patient, although fungal hyphae were detected in the mucus of all five patients. This is in agreement with the absence of eosinophilia in 66.4% of positive middle meatal lavage fungal culture in our study [14••]. Watanabe *et al.* [50] showed only in some cases of CRS, eosinophils phagocytosing the cuticle substance of the hyphae into a sheet-like invaginated space and releasing granular protein into that space in the presence of fungal hyphae. Whether this is an innate immune response or eosinophils responding *in vitro* to opsonized targets, however, the destruction of hyphae by eosinophils does not provide evidence that this is a fungal-mediated disorder.

Eosinophil counts can be elevated by other causes other than fungal etiology, e.g. allergic as well as nonallergic syndromes, most notably nonallergic rhinitis with eosinophilia and acetylsalicylic acid triad syndrome [51], or as a result of superantigenic stimulation [52,53]. In our [14••] study, eosinophilia was present in 40% of negative middle meatal lavage culture cases.

Relation of fungi to the clinical aspects of chronic rhinosinusitis

In our [14••] study, no correlation existed between fungal culture, cellular and other clinical parameters, e.g. visual analogue scale for the symptoms, nasal polyposis score or computed tomography score. Also, in another study by Murr *et al.* [27] with fungal speciation using quantitative PCR and quality-of-life survey in CRS, no significance could be ascribed to the presence or absence of fungi recovered, the type of fungi or the possible impact of fungi on the quality-of-life survey results.

Fungi and the lower airway in chronic rhinosinusitis

Fungi are ubiquitous saprophytes that reproduce by the formation of spores that are able to enter the respiratory tract by means of inhalation [36]. The positive culture rates of BAL for fungi were 28% in all CRS patients [14••]. Regardless of functional involvement of the lower airway that was observed in 60% of CRS patients, there was no significant difference between BAL fungal cultures in different lower airway involvement subgroups [14••]. Also, the positive fungal culture results did not correlate with lower airway functional changes ($P > 0.05$) [14••].

Different genus of fungi were identified in the positive BAL fungal culture (*Aspergillus* was cultured in 42.5% and *Penicillium* in 71.4%) [14••]. The process of inhalation,

retention and clearance can undoubtedly be seen from these results. The smaller size of *Penicillium* spores (below 2 μm) than *Aspergillus* (2–4 μm) than *Alternaria* (23–34 $\mu\text{m} \times 7$ –10 μm) can explain the higher culture rate of the former in the lower airways than the latter [54].

Much of what we know about the immunopathogenesis of AFS draws a strong analogy to allergic bronchopulmonary aspergillosis (ABPA). ABPA always occurs in nonimmunocompromised patients, and belongs to the hypersensitivity disorders induced by *Aspergillus* and other fungi. Most patients with ABPA have either asthma or cystic fibrosis. The inhalation of spores from the environment is followed by growth of hyphae in the mucus of the bronchial tree, and stimulates an immune response involving T helper 2 CD4⁺ T cells and IgE/IgG antibodies [55].

When there is inflammation, the natural hyporesponsiveness is lost, and so reactions to bacteria and fungi should be encountered more easily. In addition, when a chronic inflammatory condition exists, the cells may be activated nonspecifically and when they encounter an antigen or immunogenic reaction behave in such a way as to appear specifically active against the foreign substance. When the condition is more severe then, by definition, more inflammation occurs and cells will be more active.

Taken together, the immunopathology of AFS and ABPA appears similar, but not identical, suggesting a magnified immunological response in ABPA as compared to AFS.

Such observations can be applied easily in patients with asthma and CRS. Most patients with ABPA have either asthma or cystic fibrosis. When screening was performed in patients with persistent asthma, the prevalence of ABPA was between 1 and 2% [56,57]. In cystic fibrosis patients, ABPA is a common complication, occurring in approximately 10% of cases [58]; the same can be seen in AFS. Most patients had prolonged CRS with nasal polypsis. In the last survey in 20 medical units in the USA, the incidence of AFRS in CRS patients was between 0 and 23% [59].

Conclusion

Sticking to the new guidelines and recommendations for CRS can help to avoid bias in CRS studies. Involvement of the lower airway (as asthma, small airway disease and bronchial hyperresponsiveness) was determined objectively in 60% of CRS. Fungi in CRS patients are found mainly in sites where the mucus lining presents. Outstanding progress has been made in the development of better techniques to detect fungi in nasal secretions. The site and method of collection are reasons for variable study results. Fungal spores after inhalation are submerged in the aqueous lining layers of the airways.

In most CRS the process of inhalation, retention and clearance is impaired. The site of retention depends on the size of the inhaled spores. As in ABPA that occurs in asthma or cystic fibrosis, in CRS with the presence of such chronic inflammation, the cells may be activated non-specifically. When the condition is more severe then, by definition, more inflammation occurs and cells will be more active, which can explain the picture of the AFS entity. The role of fungi in CRS patients will be proved only when T cells within the sinuses are shown to be actively responding to fungal antigens cultured from the sinus and with the demonstration that their removal will end the disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 112).

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