Allergic fungal sinusitis. A naso-sinusal specific hyperreactivity for an infectious disease?

La sinusite allergica micotica. Iperreattività naso-sinusale specifica o infezione?

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Key words

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Parole chiave

Malattie dei seni paranasali • Poliposi nasale • Micosi • Sinusite allergica

Summary

Allergic fungal sinusitis (AFS) is a rare disease of naso-sinusal complex affecting mainly young, immunocompetent adults who complain of chronic rhinitis and/or recurrent nasal polyposis despite medical and/or surgical treatment. Aim of the study is to analyse, from an allergological and otorhinolaryngological point of view, patients affected by the so-called "allergic fungal sinusitis" in order to better define the relationship between fungi present in naso-sinusal secretions and the host's immunoreactivity. From February 2001 to January 2002, 24 selected patients (13 male 11 female) age range 25-65 years (mean 45), with chronic rhinosinusitis, with a positive fungal examination of nasal secretion, underwent allergological evaluation. All patients were positive for diagnostic criteria of allergic fungal sinusitis and, in all patients, nasal lavage was performed for microscopic examination by fluorescence. Samples were then cultured on Sabouraud growth media for identification of the fungus. Skin prick tests (SPT) were then performed with the 15 main inhalant allergens and twelve fungal allergens (Bracco). The total IgE serum level (PRIST), the specific fungal IgE and the eosinophilic cationic protein were then investigated by means of an immuno-fluorine enzymatic method. Finally, a nasal provocation test was carried out with diluted solutions (1/100, 1/10) and with a pure solution of fungal allergens, selected according to microbiological examination of nasal secretion of each subject. Prick tests were positive for seasonal and perennial allergens in 5 patients (21%), while prick tests with fungi were positive in only 4 patients (16.6%). Total IgE levels were higher than in normals (200 KU/l) in 6 patients (25%) (mean 364.74 KU/l). In another 18 patients, total IgE were normal. Specific IgE levels for the tested fungi and eosinophilic cationic protein levels were within normal range in all patients. Nasal provocation test was negative in all patients. Presence of fungi in nasal secretions of patients with AFS does not appear to be correlated with an allergic status to the isolated fungus. A role for IgE in either the aetiology or the pathophysiology of allergic fungal sinusitis is unlikely, and probably the diagnostic criteria for allergic fungal sinusitis should not include type I hypersensitivity, since no confirmed evidence exists that IgE-mediated type I hypersensitivity is involved in the pathophysiology of allergic fungal sinusitis.

Riassunto

La sinusite allergica micotica (SAM) è una rara affezione del complesso naso-sinusale che colpisce prevalentemente soggetti giovani, immunocompetenti, e che si presenta sotto forma di una rinosinusite cronica. Nella maggioranza dei casi è associata a polipi nasali, con alto tasso di recidiva nonostante i vari trattamenti medici e/o chirurgici instaurati. L'incidenza della sinusite allergica micotica nella rinosinusite cronica iperplastica trattata chirurgicamente oscilla, come riportato in letteratura, tra il 6% ed il 13% dei casi. I polipi nasali e l'asma incidono invece, rispettivamente, nel 75% e nel 65% dei casi riportati in letteratura. Scopo del presente lavoro è quello di analizzare dal punto di vista otorinolaringoiatrico ed allergologico un gruppo di pazienti selezionati sulla base di criteri diagnostici riportati in letteratura e suggestivi di sinusite allergica micotica, nel tentativo di meglio definire le relazioni etiopatogenetiche tra la presenza di micofiti nel liquido di lavaggio nasale e l'immunoreattività del paziente. Dal febbraio 2001 al gennaio 2002 abbiamo selezionato 24 pazienti (13 uomini ed 11 donne) di età compresa tra i 25 ed i 65 anni (età media 45 anni) affetti da rinosinusite cronica polipoide micotica sulla base delle evidenze cliniche, endoscopiche e microbiologiche. Tutti i pazienti studiati sono stati sottoposti ad esame allergologico mediante "skin prick test" con un pannello di 15 allergeni inalanti e 12 estratti micotici. Sono state inoltre dosate in tutti i pazienti le IgE totali (PRIST), le IgE specifiche e la proteina cationica degli eosinofili. Infine i pazienti sono stati sottoposti a test di provocazione nasale con soluzioni contenenti l'estratto allergenico del micofita isolato nel liquido di lavaggio nasale. Le cutireazioni sono risultate positive per allergeni stagionali e perenni in 5 pazienti (21%), e per estratti micotici in 4 pazienti (16,6%). Il valore delle IgE totali è risultato superiore alla norma in 6 pazienti (25%), le IgE specifiche sono risultate assenti in tutti i casi studiati, così come la proteina cationica degli eosinofili ed il test di provocazione nasale micofita-relato. I risultati ottenuti dal nostro studio ci permettono di affermare che la presenza di funghi nelle secrezioni nasali di pazienti affetti da rinosinusite allergica micotica non sembra potersi correlare ad uno stato allergico/iperergico nei confronti del fungo isolato. Il ruolo di meccanismi IgE-mediati nell'etiologia e nella fisiopatologia della sinusite allergica micotica non sembra ancora potersi confermare, anche se ulteriori studi sono necessari per la definizione di questo problema.

Introduction

Currently, most rhinologists recognise 4 types of fungal sinusitis: acute/fulminant (invasive), chronic/indolent (invasive), mycetoma (fungus ball) and allergic fungal sinusitis (AFS) (Tab. I). The first type is the only form of acute fungal sinusitis. It occurs exclusively in diabetic or immunosuppressed patients, most typically in oncological or transplanted patients. Fungal cultures usually reveal Phycomycetes (*Mucor* or *Rhizopus*), *Candida* or *Aspergillus* species. Chronic/indolent invasive fungal sinusitis occurs in immunocompetent individuals who usually have a long-standing history of rhinosinusitis. The disease progresses slowly, producing chronic granulomatous inflammation and extension beyond the sinus walls. *Aspergillus* species and members of the *Dematiaceous* family are the most frequent causative organisms. Mycetoma or fungus ball affects immunocompetent, non-atopic patients and the disease may involve any sinus, but usually occurs in a single sinus, most frequently the maxillary antrum. Bone erosion and mucosal invasion does not occur. The lack of sinus inflammation distinguishes this disorder from other forms of chronic fungal sinusitis. The aetiologic organism is almost always *Aspergillus fumigatus*.

AFS was first described in the early 1980s when Millar et al. [1] recognised immunologic and histologic similarities between the specimens obtained from the maxillary sinuses of 5 patients and those of Allergic Bronchopulmonary Aspergillosis (ABPA). Katzenstein et al. [2] then retrospectively reviewed 119 histologic specimens obtained from patients who had previously undergone sinus surgery. They found 7 cases with mucin-containing eosinophils, Charcot-Leyden crystals and fungal hyphae, histologically resembling ABPA and called this entity Allergic *Aspergillus* Sinusitis. Since 1989 [3-5], as it became apparent that *Dematiaceous* fungi and not *Aspergillus* (only 15% of cases), were the primary aetiologic agents, the name was changed to AFS. Indeed, *bipolaris spicifera* was the most commonly isolated fungus, with a prevalence of 67%. Other species of the *Dematiaceous* family include *drechslera*, *alternaria*, *curvularia*, *exserophilum*, *rhizopus*, *fusarium* [6-11].

Although this entity is more frequently recognised, today, it is still presumably underdiagnosed [11]. Warm humid climates seem to foster fungal proliferation. The prevalence in the population of patients requiring surgery for chronic sinusitis is currently estimated to range between 6% and 13%, with a slight prevalence in males (ratio 1.6), with no ethnic differences. The typical AFS patient is a young - 23-42-years-old - immunocompetent, atopic adult with chronic sinusitis [12-14], and, in most reported cases, atopy and asthma are present. The incidence of asthma ranges from 30% to 100% of cases [15 16], Aspirin intolerance is present in 27% of cases [16]; nasal polyposis is a common feature, with an incidence ranging from 75% to 100% of cases [17 18]. Even if nasal polyposis is not a specific marker of chronic nasal inflammation, the incidence of AFS ranges from 5% to 10% in patients submitted to surgery for sinonasal polyposis [18]. Patients typically report a history of sinonasal polyposis, recurrent sinusitis and numerous surgical procedures. Sinusitis is usually refractory to antibacterial treatment. While the initial signs and symptoms are those typical of polypoid rhinosinusitis, orbital proptosis, malar deformities, mucoceles and diplopia are occasionally seen. Inflammation, usually, affects all paranasal sinuses, but may, at times, be asymmetric involving only one side. In 75% of cases, patients complain of the presence of a characteristic "so-called" allergic mucus, which is thick and viscous and often stained

Table I. Clinical and diagnostic features of fungal sinusitis.

Type	Immune status	Fungal role
Acute/fulminant	Compromised	Pathogen
Chronic/indolent	Competent	Pathogen
Mycetoma (fungus ball)	Competent, non atopic	Saprophyte
Allergic fungal sinusitis (AFS)	Competent, atopic	Allergen (?), saprophyte (?)
Tissue invasion	**Sinusal involvement**	**Course**
Yes	Single	Acute
Yes	Variable	Sub-acute
No	Single	Chronic
No	Multiple, unilateral	Chronic

Table II. Diagnostic features suggesting AFS.

Major diagnostic criteria
Positivity of allergological examination for fungi (skin prick tests and/or RAST and/or nasal provocation test). Identification of allergic mucin by rhinoscopy either at time of sinus surgery or later on histopathologic evaluation of material from sinus, containing fungal hyphae, dense accumulations of eosinophils with Charcot-Leyden crystals and necrotic cellular debris. Demonstration of fungal elements in nasal discharge or in material obtained by nasal lavage or at time of surgery by stain or culture.
Minor diagnostic criteria
Chronic rhino-sinusitis (endoscopic and/or peroperative demonstration). Presence at CT scan of serpiginous areas of high attenuation especially in ethmoidal and maxillary sinuses, with bone thinning and erosions with dislocation of adjacent structures. Presence at Magnetic Resonance images of areas showing decreased signal intensity leading to hypointense T1-weighted and markedly hypointense T2-weighted images with typical void signal.

From Bent and Khun [11], 1994 (modified).

brown, yellow or green due to bacterial superinfection or fungal material.

Histologic observation of the surgical specimen reveals a triad of eosinophilia, Charcot-Leyden crystals and extramucosal hyphae. Charcot-Leyden crystals are simply a byproduct of necrotic eosinophils such as phospholipases. Hyphae can usually be seen with haematoxylin-eosin (HE) or potassium-hydroxide stains, with PAS technique and, if necessary, special stains such as Gomori methenamine silver (GMS) [19]. The presence of fungi in the mucin but not in the tissues of AFS patients differentiates AFS from chronic invasive fungal sinusitis. By definition fungal invasion does not occur in any case of AFS [19] and for this reason, most Authors believe that the method of choice for identification of fungi in AFS is represented by the collection of nasal fluids by means of a correctly performed nasal lavage [19 20]. With particular stains, such as "Fontana-Masson", it is possible to reveal the presence of melanine, a typical element of the *Dematiaceous* fungi.

Total serum IgE levels are generally elevated, although less than with ABPA. Sometimes, peripheral eosinophilia and/or fungal-specific IgE are present. In 60% of cases, skin test reactivity to a broad range of commercial fungal extracts can be demonstrated [20-23]. According to some Authors, it is possible to reveal positivity to skin prick tests (SPT) and the presence of fungal-specific IgE for at least one commercial fungal extract of the *Dematiaceous* group in 100% of patients with AFS. On the contrary, this positivity can be found in only 5% to 20% of normal individuals [15]. Our study does not support these conclusions, that were based upon a limited number of patients (8 cases) and, therefore, without statistical significance.

At computerised tomography (CT) fungi release ferromagnetic elements (magnesium and calcium) creating a serpiginous area of high attenuation, especially in the ethmoidal and maxillary sinuses [13 24]. Bone thinning and erosions with dislocation of the adjacent structures, due to expanding inflammatory tissues, can be observed. As far as concerns Magnetic Resonance Imaging (MRI) the ferromagnetic elements show decreased signal intensity, leading to hypointense T1-weighted, and markedly hypointense T2-weighted, images with a typical void signal. Some surgeons recommend MRI as the imaging investigation of choice, even if CT scan provides better bone definition.

The diagnosis of AFS is based, especially for those Authors who support an allergic origin, upon typical elements (Table II) [11]. This Table summarises the main diagnostic criteria required for the diagnosis of AFS, as presently recognised in the literature following Bent and Khun's classification study, in 1994. It would be better to divide these into major criteria, relevant to reach a definite diagnosis, and minor criteria such as diagnostic complements (as described in Table II).

Aim of the present investigation is to analyse, from an allergological point of view, patients affected by the "so-called" AFS in order to better define the relationship between the fungi present in their naso-sinusal secretions and the host's immunoreactivity.

Materials and methods

From February 2001 to January 2002, 24 adult AFS patients (11 female, 13 male), aged between 25 and 65 years, were examined from an allergological point of view.

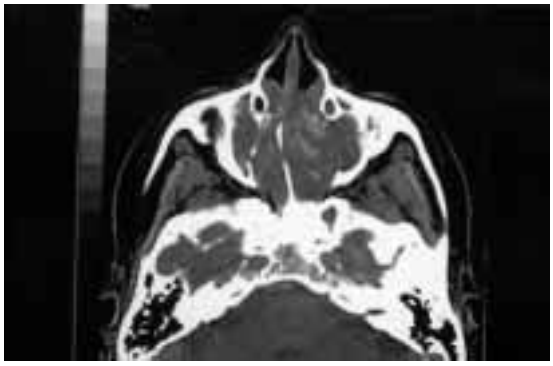

Fig. 1. CT scan in axial plane showing presence of serpiginous areas of high attenuation especially in the ethmoidal region, due to fungal release of ferromagnetic elements (magnesium and calcium).

Diagnosis was based upon medical history, clinical, endoscopic and imaging findings (Fig. 1). In this study population, 5 (20.8%) patients (4 M, 1 F) were affected by respiratory allergy, with seasonal (1 case), perennial (2 cases) and mixed perennial and seasonal (2 cases) allergic rhinitis; 5 (20.8%) patients (3 M, 2 F) presented an association of nasal polyposis with asthma and aspirin intolerance [Aspirin disease or ASA (Acetylsalicylic) Triad].

The clinical and endoscopic examination of the patients revealed the presence of bilateral nasal polyps with near total obstruction of the nose. CT scan confirmed the presence of a serpiginous area of high attenuation, especially in the ethmoidal and maxillary sinuses (Fig. 1). In 12 patients, bone thinning and erosion, with dislocation of adjacent structures, due to expanding inflammatory tissue, were observed. MR scan confirmed the presence of micotic sinusitis with decreased signal intensity, leading to hypointense T1-weighted, and a markedly hypointense T2-weighted, images with a typical void signal (Figs. 2, 3). All patients underwent endonasal lavage and specimens were collected for cytology and microbiological cultures. Using the Ponikau technique (Ponikau et al. [27]), two puffs of phenylephrine hydrochloride 1% were sprayed into each nostril to induce vasoconstriction. The spray also increased the nasal lumen and, consequently, the amount of secretion collected. After 3 minutes, each nostril was flushed with 20 ml of sterile saline, using a sterile syringe with a sterile curved blunt needle. The patients took a deep breath before injection of saline and then forcefully exhaled through the nose during flushing. The return was collected in a sterile pan. The fluid was then placed in centrifuge tubes and sent directly to the mycology laboratory where the specimens were processed under a laminar flow hood to prevent contamination. The resultant sediment was inoculated on a Sabouraud Dextrose agar slant, with or without antibiotics, on a Brain-heart infusion agar slant and on a Bacto agar BCG plate, for the development of yeasts (Fig. 4). The slants were incubated at 30°C for a period of 30 days and the plates at 37°C for one week.

All patients underwent antero-posterior ethmoidectomy with maxillar antrostomy. During the operation, the typical viscous, yellow mucous was found,

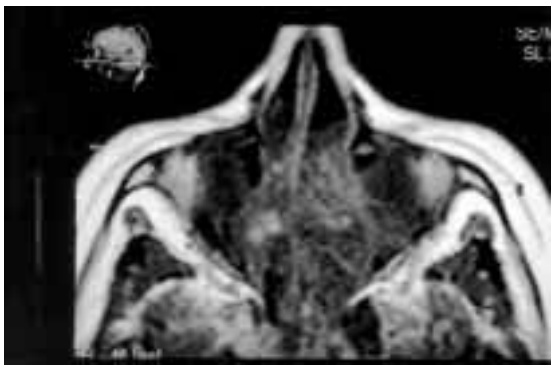

Fig. 2. T2-weighted RM scan in axial plane showing presence of hypointense images with typical void signal.

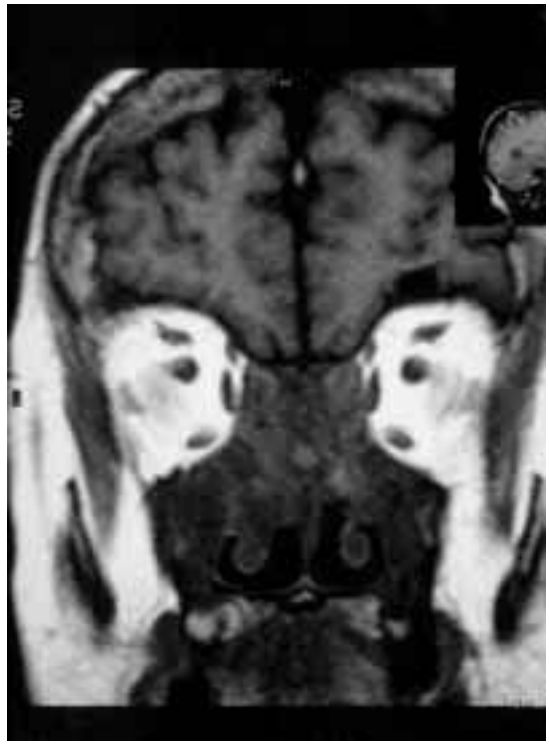

Fig. 3. T2-weighted RM scan in coronal plane showing characteristic hypointense lesions in the ethmoidal region with typical void signal.

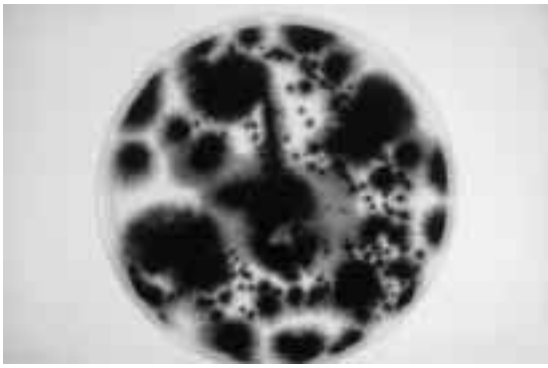

Fig. 4. Slight culture in AGAR showing *Aspergillus fumigatus* colonies.

containing eosinophils, Charcot-Leyden crystals and, in 12 patients, extramucosal hyphae (8 patients with Gomori stains, 4 with PAS technique). No fungal mucosal invasion was detected. Patients were enrolled in the study, based upon these findings and upon the major diagnostic criteria of AFS. The allergological evaluation started with SPT, using a needle in singleton, with sites spaced at least 5 cm apart. For SPT, a panel of 15 inhalant allergens (Bracco Pharmaceuticals, Allergy Division *Dermatophagoides f.* and pt., Graminaceae, *Parietaria judaica* and *officinalis*, *Plantago i.*, *Ambrosia*, *Olea*, *Cupressus*, *Alnus*, *Betulae*, *Corylus*, Ragweed, Cat and Dog dandruff), histamine, glycerosaline controls (ALK-Abellò), and the following 12 fungal allergen extract (Bracco Pharmaceuticals, Allergy Division): 1) *Stemphjlium b.*, 2) *Aspergillus f.*, 3) *Mucor mix*, 4) *Penicillium n.*, 5) *Chetomium o.*, 6) *Epicoccum p.*, 7) *Rhizopus n.*, 8) *Botrytis s.*, 9) *Candida a.*, 10) *Alternaria f.*, 11) *Cladosporium*, 12) *Helminthosporium s.* were used. A positive test was defined as a wheal > 3 mm in diameter compared with the negative control and with surrounding erythema and oedema. The PRIST, the specific fungal IgE and the eosinophilic cationic protein (ECP)were then investigated by means of an immuno-fluorine enzymatic immuno assay (FEIA Cap System Pharmacia, Stockholm, Sweden). The normal values were considered < 200 KU/l for PRIST, values ranging from 0 to 0.75 KU/l for RAST and < 20 mcg/l for ECP.
Finally, a nasal provocation test (NPT) was performed both with progressively diluted solutions (1/100, 1/10) and with a pure solution of fungal allergens, selected according to the results of the nasal secretion examination.
Nasal provocation test was carried out with allergenic extract containing 1250 SBE (Standardisierte Biologiche Einheiten or BU, Biologic Unit). The test starts with the topical nasal administration of 0.04-0.05 ml of Chloruro-saline solution with diluted phenol acid. The first nasal response was recorded after 15, 30 and 45 minutes by means of active anterior rhinomanometry with analysis of nasal resistances. The absence of increased nasal resistance > 20% was considered a negative response to stimulation, excluding the presence of aspecific nasal hyperreactivity. Specific allergic stimulation was carried out using 0.04-0.05 ml of a mycotic allergic extract with 2 BU/ml, 4 BU/ml and 8 BU/ml concentrations at intervals of 15, 30 and 45 minutes. A ≥ 20% increase in nasal resistances was considered a positive response to stimulation.

Results

The collected nasal fluids showed, in all cases, mucin containing inflammatory cells such as basophils, eosinophils and mast cells, as well as Charcot-Leyden crystals.
SPT was positive for seasonal and perennial allergens in 5 patients (20.8%), while SPT for fungi was positive in only 4 patients (16.6%), 2 for *Alternaria* (8.3%), 1 for *Penicillum n.* (4.1%) and 1 for *Rhizopus* (4.2%). Total IgE levels exceeded normal values (200 KU/l) in only 6 patients (25%) (mean value 364.74 KU/l). In the remaining 18 cases, the value of PRIST was normal (mean value 107.5 KU/l). No specific fungal IgE was found for the fungi tested. ECP levels were normal in 23 out of 24 patients (<20 mcg/l). Only in 1 patient was the ECP level 41.4 mcg/l. NPT was negative in all the patients studied. The microbiological evaluation of nasal secretions revealed the presence of fungi in all enrolled patients; the following fungi have been identified: *Aspergillus f.* (no. 8), *Penicillium n.* (no. 7), *Penicillium n.* and *Aspergillus f.* (no. 2), *Alternaria t.* (no. 4), *Mucor m.* (no. 1), *Rhizopus n.* (no. 1), *Cladosporium* (no. 1).

Discussion and conclusions

In the present study, evidence of fungi was found, in the nasal fluid of all enrolled patients, but only 4 (16.6%) showed a positive SPT for fungi, even with negative RAST and NPT.
The pathogenesis of AFS remains to be fully elucidated. Much controversy exists, in the literature, concerning the role that hypersensitivity (Gell and Coombs type I IgE-mediated and type III-immunocomplex-mediated responses) play in this disease. According to most Authors, fungi presumably become entrapped in the sinuses of allergic subjects resulting in an osteomeatal complex obstruction, extremely thick mucus and a mucociliary clearance disor-

der. The ensuing immune response exacerbates the disease [25].

Results of the present investigation appear to confirm the saprophytic role of fungi. In fact, although 100% of our patients showed microbiological positivity for different fungal species, only 16.6% of them showed a positive SPT for fungi and PRIST values were positive in only 25% of cases; no specific fungal IgE was found and the NPT performed both with progressively diluted solutions (1/100, 1/10) and with a pure solution of fungal allergens, selected according to the result of the nasal secretion microbiological examination, was negative.

Positivity to allergological tests reported by many Authors, for various species of fungi is, in our opinion, not a reliable criterion, since, in the general atopic population, a large percentage shows mild positivity for fungal allergens without any clinical signs of sensitisation [26].

We agree with the Authors who state that the sensitivity and specificity of total and specific IgE, in AFS, are unknown, and that the reliability of these tests in determining prognosis or efficiency of treatment is uncertain [16]. It is possible that local IgE production, in the nasal mucosa, could be increased without elevated blood IgE levels to fungi. Even with an elevated local IgE production, an IgE-mediated type I hypersensitivity reaction to fungi requires mast cells degranulation. But mast cells are not increased in the nasal mucosa or in the nasal mucus itself in AFS patients [27]. In this regard, it should be pointed out that the issue of local IgE production, in the nasal mucosa, has been a matter of controversy ever since the discovery of IgE 35 years ago. All the requirements for production of IgE are present at nasal level. For example, the presence of antigen-processing and antigen-presenting cells, T- and B-cells, interleukins (IL-a, IL-13) are important for the IgE switch. On the other hand, it is also true that human nasal mucosa lacks lymphoid tissue and germinal centres. The specific IgE levels are generally higher in nasal secretions than in serum. Although this finding may indicate a local production of nasal IgE, the accumulation of IgE-producing cells, in the nose, could alone justify these findings. Immunohistochemical studies,for the detection of IgE on mucous plasma cells, are complex and have not yet presented any conclusive evidence. As far as local nasal production of IgE is concerned there are two important conclusions. If the local production of IgE, in the nasal mucosa is confirmed, local treatment becomes very important, and the observation of negative allergological test in patient with signs of allergic rhinitis could be explained by an immune reaction strictly confined to the nose. On the other hand, we should consider NPT as a diagnostic tool, especially when positive. The negative or uncertain response to a nasal provocation test could be explained by the presence of a minimal level of nasal IgE, insufficient to stimulate an immunoreaction. It is clear, however, that further research is necessary to investigate the nasal immune reaction mechanisms and definitively validate nasal allergodiagnostic tests.

Basing upon these considerations, the pathogenetic role of an hypothetical allergy to fungi is, in our opinion, still not demonstrated. Probably, the increased fungus-specific IgE levels found in some AFS patients could be due to a recognition of fungi by the immune system or to the presence of an associated allergic rhinitis and may not be the primary cause of the disease.

In view of these considerations, we believe that the diagnostic criteria for AFS should be classified as major and minor as reported in Table II.

Based upon these criteria, in the present investigation only in 16.6% of the patients there was an evident immunological involvement which could sustain a role of allergy to fungi in the pathogenesis of AFS. The diagnostic tool for AFS should be the microbiological examination of nasal secretions, especially in those cases with few fungal hyphae, not detected with routine histological techniques (H&E, PAS).

Another aspect worthy of attention is the immunoreactive role of fungi in the genesis of nasal polyposis. Albeit the small size of the tested group of patients (24), the even smaller group of patients who way positive atthe mycophyte prick test (4) and the very small number of commercially available mycophytes in comparison to those theoretically responsible for hyperphonetic respiratory disorders, allow us only to hypothesise that the fungi, especially those that are not normally saprophytes of the nasosinusal region, could play a significant pathogenetic role in nasal polyposis.

In conclusion, in our opinion, although physiopathological mechanisms underlying AFS still remain to be fully elucidated, there is increasing evidence that fungi play mainly a saprophytic role and that they represent an important inflammatory stimulus rather than a clearcut allergenic effect. The allergenic role of many fungi is still uncertain and difficult to identify also due to the lack of availability of purified fungal extracts both for “in vivo” and “in vitro” tests, but the issue is still unsolved and further studies are necessary in order to better understand the real nature of AFS and the therapeutic implications. At present, even if the physiopathological mechanisms involved in AFS still remain to be defined and controversial theories exist regarding the allergenic or infectious nature of the disease, there is, in our opinion, mounting evidence demonstrating the saprophytic role of fungi, even if further research is required to define the exact nature of this disease and its implications from a therapeutic point of view.

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