

EDITORIAL

Refractory rhinosinusitis: possibly fungal matter?

The nose is a prominent facial characteristic that helps to define an individual's appearance, yet in contrast to its external aspects, we know much less about common conditions that afflict its interior. The upper airways incorporate the paranasal sinuses as well as the nasal cavities and these inner spaces seem to react in concert more often than we might think, for example in the common cold, where up to 90% of cases also involve the sinuses [1]. The general classification of rhinosinusitis divides the disease into allergic and non-allergic rhinitis/rhinosinusitis. The allergic forms include intermittent/seasonal, persistent/perennial or occupational and the non-allergic forms may be infectious, drug-induced, hormonally conditioned or idiopathic. These denominations reflect the current knowledge of aetiology. To reach a correct diagnosis, a meticulous clinical investigation has to be performed complemented by tests and imaging [2].

Current therapies, whether pharmaceutical, surgical, or a combination, rarely provide a permanent solution to several of the sinonasal conditions, and a recurrent aim in developing better therapies is to elucidate the inflammatory and immunological mechanisms of these different forms of rhinosinusitis. In rhinosinusitis research, the immunopathology of allergic (atopic) forms of the disease has been the more thoroughly investigated area, often analogous to asthma research. In atopic disease, both genetic and environmental factors influence aberrant type 2 T helper (Th2) cell activity [3]. The inflammatory process may be initiated by interaction of allergen with immunoglobulin (Ig)E bound to mast cells or basophils, and Th2-type cytokines and chemokines characteristically also induce eosinophilia [3].

Among the non-allergic forms of rhinosinusitis, some have clearly defined causes such as rhinitis medicamentosa, hormonal rhinosinusitis (as may occur in pregnancy or oral contraceptive use), and acute bacterial sinusitis, and the options of action may also be clear. Non-allergic forms of rhinosinusitis also includes the idiopathic form, which may occur with or without nasal polyps. The idiopathic form is chronic and refractory to treatment, and developing a better understanding of this form of rhinosinusitis remains a challenge. It is likely that it reflects a syndrome of different diseases and causative factors.

Idiopathic (or perennial non-allergic) rhinosinusitis can be further classified as non-allergic rhinitis with eosinophilia (NARES) [4], which may be linked to the expression

of polyps [5], and non-eosinophilic non-allergic rhinitis (NENAR) [6]. In NENAR, which lacks, by definition, the characteristic eosinophilic response, abnormalities in local autonomic nasal reflexes have been suggested as the cause [6]. Results in this field should lead to a recommendation to outpatients, in this category, to keep their feet warm to prevent nasal congestion [7].

Eosinophilic infiltration in polyps and/or mucosal tissue in non-allergic rhinosinusitis patients has been evaluated and local production of specific IgE was described in the 1980s [8]. More recently, studies have identified the essential similarity of the inflammatory cascade in patients with allergic rhinosinusitis and in those patients with idiopathic rhinosinusitis that lack the systemic markers of atopy [9]. Evidence of Th2 cell involvement in idiopathic as well as allergic rhinosinusitis has been reported [10], raising the hypothesis of a local, demarcated and non-systemic allergy in the sinonasal region.

The role of bacteria in chronic rhinosinusitis has to be further investigated. The so called, normal bacterial flora of the nose may be the normal flora solely under healthy conditions. If so, a normal bacterial flora, which is bacteria not being the origin of disease, may change with different nasal disorders. The question is then, how to evaluate normally considered, pathogenic bacteria, which can be found under aberrant nasal conditions of chronic and refractory rhinosinusitis without an infectious exacerbation [11]. Antibiotics should be used only if necessary. But do we know when that is? It is important to find alternatives to antibiotics to be able to regulate the bacterial flora. Ideally, preventive measures to normalize the microenvironment in the sinonasal cavities would be available to encourage colonization by non-pathogenic bacteria, as persistent antibiotic therapy risks the emergence of drug-resistant bacteria and does not guarantee against a new colonization of pathogenic bacteria.

Bacteria may act as local or systemic antigens, and several bacterial species implicated in chronic sinonasal disease are potent inducers of IgE. Bacteria-specific serum IgE can be quantified as described and can be verified in idiopathic rhinosinusitis patients, in contrast to those with allergic rhinosinusitis [12]. These results give a prospect of future combination therapy with immediate eradication of bacteria (antibiotics or other alternative) followed by desensitization. Growing research in *Staphylococcus aureus* points in this direction. Patients with *S. aureus* strains

that produce superantigens (enterotoxins), when compared to those patients without the superantigen-producing type of *S aureus*, have more severe sinonasal symptoms, as measured by symptom score [13]. Recently, specific IgE directed against *S aureus* enterotoxin, in combination with high total IgE concentrations, have been found locally in eosinophilic nasal polyps, in the absence of corresponding systemic IgE or skin prick tests [14]. Again, the evidence points towards a local, demarcated and non-systemic allergic response.

In the search for better diagnosis and more appropriate therapy of refractory rhinosinusitis, there has been increasing interest in non-invasive variants of fungal disease in the sinonasal region in the last decade. This originated in the early 1980s with the recognition of 'allergic *Aspergillus* sinusitis' as a histopathological corollary to allergic bronchopulmonary aspergillosis (ABPA) [15]. ABPA is due to type I and III hypersensitivity reactions to the fungus *Aspergillus fumigatus* in the lower airways of patients with chronic asthma or cystic fibrosis. This fungus is ubiquitous in soil and decaying organic matter, and its spores, which can reach airborne levels several times higher than the pollen counts, enter the human body by inhalation. As in fungal diseases in general in immunocompetent patients, the prevalence of *A fumigatus* is dependent on the climate; both ABPA and allergic fungal rhinosinusitis (AFRS) are more prevalent in warm climates [16,17]. The combination of AFRS and allergic rhinosinusitis is common, 84%, but not obligatory [18] and, thus, might represent a possible cause of NARES.

The bronchopulmonary expression of *A fumigatus* is caused by its release of virulence factors and proteases. The reaction displays impaired mucociliary clearance, impaired action of fungicidal proteins and complement in the airway lining fluid, inhibition of phagocytosis and the killing capacity of phagocytic cells (macrophages, neutrophils), and degradation of extracellular matrix proteins [19]. The inflammatory response to ABPA resembles uncomplicated asthma with Th2-type cytokines regulating the eosinophil infiltrate along with thickening of the epithelial basement membrane and smooth muscle hypertrophy, but the expression is more pronounced in ABPA, with a dilatation of the proximal bronchi filled with inspissated mucus plugs containing eosinophils, Charcot-Leyden crystals, Curshmann's spirals and, usually, fungal hyphae. The sinonasal appearance is similar, with chronic eosinophilic inflammation in the mucosa and the diseased sinuses filled with eosinophilic (so-called allergic) mucin with a peanut butter consistency that contains the same matter as the bronchial plugs [20]. Almost always, obstructive nasal polyposis is present [18].

The distribution of non-invasive *Aspergillus* allergic disease is of great interest. If an individual is predisposed to *Aspergillus* colonization at one site, then is s/he likely to

have *Aspergillus* in other sites? Very few studies have been performed to answer this question, so the results of the comprehensive study performed by A. Shah and his colleagues in this issue [21] are timely and topical. The study investigated the prevalence of cases of parallel allergic *Aspergillus* rhinosinusitis in patients with ABPA. Among 95 patients with ABPA, over one-third (38) had sinonasal symptoms. Radiological evidence of sinus involvement was found in 17 of the 38, and, moreover, in 5 of the non-symptomatic patients. Of the total 22 possible cases, 13 declined the surgical intervention that currently is necessary for the full diagnosis [20]. However, of the 9 patients with ABPA, sinonasal symptoms, and pathologic sinus X-ray, allergic *Aspergillus* rhinosinusitis was confirmed postoperatively in 7. This leads to the conclusion that currently, in India, 78% (7/9) of patients with ABPA, sinonasal symptoms and pathologic sinus X-ray, also have allergic *Aspergillus* rhinosinusitis. Thus, every new ABPA case should routinely have their sinonasal region investigated, but new non-invasive methods to screen for sinonasal onset in previously sensitized ABPA patients are needed.

Recent studies in AFRS have demonstrated involvement of a surprisingly large number of fungal species, including other *Aspergillus* spp. as well as *Curvularia*, *Bipolaris*, and *Alternaria* among others [18]. The dematiaceous (pigmented) fungi seem to be the more common agents. However, the overall picture remains somewhat confusing. Patients with AFRS who have a positive skin prick test result to fungal antigens appear to be positive to every fungus antigen tested [22], but this is perhaps consistent with the very wide variety of fungal species identified in nasal lavage fluid from individuals with refractory rhinosinusitis as well as healthy controls [23]. Methods based on polymerase chain reaction (PCR) produce significantly more positive samples, and as PCR only requires an amount of DNA equivalent to 10 or fewer fungal elements [24] it should find a wider place in future research and diagnosis both in AFRS and eosinophilic mucin rhinosinusitis (EMRS). AFRS patients tend to be younger immunocompetent individuals, while EMRS occurs more commonly in older patients, who often also have asthma [25]. An extended investigation demonstrated significant clinical and immunological differences between EMRS, postulated to be a systemic disease, and AFRS [18]. A higher proportion of EMRS patients showed aspirin-sensitivity (54%) compared to AFRS patients (13%), and all EMRS patients had bilateral disease compared to only 55% of AFRS patients [18].

Future research in non-invasive fungal disease promises to be interesting and a great deal more needs to be learnt and applied clinically. With respect to diagnostic methods, measurements of inflammatory mediators that amplify fungal pathogenicity might be possible, as well as

investigations of genetic and other factors that may predispose patients to these conditions. Therapeutically, there is a clear need for better agents to eradicate fungal colonization, whether infectious or not, to effect a permanent cure. Various azoles have been assessed as alternatives to amphotericin B [26], and corticosteroids, both topical and oral, are necessary as well as surgical measures [21]. Immunotherapy is also under development [27] and may complement pharmacological approaches. To be practical, why not use a face-mask daily to avoid fungal spore confrontation under desensitization and anti-fungal therapy?

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