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Romanian Journal of Rhinology, Vol. 7, No. 26, April-June 2017 DOI: 10.1515/rjr-2017-0008

LITERATURE REVIEW

Noninvasive fungal rhinosinusitis

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ABSTRACT

Fungus ball (FB) of the paranasal sinuses has a distinctive clinicopathological presentation. The disease occurs more frequently in elderly patients and has a female preponderance. Classically, it involves only one paranasal sinus in more than 90% of the cases, most commonly the maxillary sinus. Imaging characteristics (calcifications and / or erosion of the inner wall of the sinus visible on CT) and histopathological ones (luminal aggregation of fungal hyphae) confirm the diagnosis.

Allergic fungal rhinosinusitis (AFRS) usually occurs in younger, immunocompetent patients, with a history of atopy, including allergic rhinitis and / or asthma, or a long clinical picture of chronic rhinosinusitis (CRS), refractory to antibiotic treatment. Nasal polyps (NP) are present in almost all patients, while extra-sinusal complications are described only in some of them. Usually, there is involvement of several sinuses, as well as bilateral damage. The definitive diagnosis is confirmed only by examining surgical specimens - the characteristic appearance of eosinophilic mucin is the most reliable indicator of AFRS.

KEYWORDS: fungal rhinosinusitis, fungus ball, allergic fungal rhinosinusitis, eosinophilic fungal rhinosinusitis, eosinophilic mucin rhinosinusitis.

INTRODUCTION

The incidence of fungal rhinosinusitis (FRS) in the immunocompetent population has increased during the last decades. The recent increase in the incidence of these disorders is due to the improvement of diagnostic methods, especially the new imaging techniques (CT, magnetic resonance imaging - MRI) and the expansion of conditions facilitating fungal infections (diabetes mellitus, long-term treatment with antibiotics, corticosteroids and immunosuppressants, radiotherapy, chemotherapy, disorders that associate immunodeficiencies). However, many authors suggest that fungal infection of the paranasal cavities are discovered more frequently in healthy patients. This confirms the existence and persistence of local factors favouring the development of FRS[1].

Although the classification is still equivocal, each of the clinicopathological variants of FRS is associated with geographical risk factors, host risk factors and different fungal etiologic agents. Therefore, understanding the different types of FRS and knowing the clinico-anamnestic, imaging, microbiological and histopathological particular features have a crucial role in using the appropriate techniques to confirm the diagnosis. The prompt diagnosis and initiating the appropriate therapy are essential to avoid any late consequences, complications or fatal results[2,3].

FRS are divided into two categories based on histopathological findings – non-invasive and invasive. "Invasiveness" refers to the invasion of the mucosa and sinus bone, the expansion into adjacent structures and tissues. Noninvasive FRS are subdivided in saprophytic fungal infections, FB (fungus ball) and eosinophil-related FRS (allergic FRS, eosinophilic mucin rhinosinusitis and eosinophilic FRS)[2].

Local saprophytic colonization refers to the asymptomatic fungal infestation of the rhinosinusal mucosa, common in patients who have undergone previous sinus surgery. The increasing possibility can lead to the FB formation. Nevertheless, most patients with local fungal colonization rarely show clinical symptoms; usually, they are asymptomatic, have a benign evolution and treatment is not necessary[2,4,5].

FUNGUS BALL

Fungus ball is a relatively less frequent form of FRS, noninvasive, less or not at all aggressive. According to recent recommendations of scientists, using the old nonspecific terms of "aspergillosis", "aspergilloma" and "mycetoma" is not appropriate[3,6-8].

FB commonly appears in normal immunocompetent persons, at 60-70 years of age, although, in some retrospective studies, age ranged within 14-87 years. There is a

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considerable and constant predilection for females of about 57-64%, with a ratio of 1.5-1.9:1 between men and women[4,9,10].

Usually, the disorder is unilateral, involving only one sinus (up to 90-99% of the cases). The most common site is the maxillary sinus (78-94%), followed by the sphenoid sinus (4-15%). Ethmoid sinuses involvement (1-15%) is often associated with the maxillary sinus pathology, frontal sinus involvement being much rarer. Multi-sinus localization was found only in 6-41% of the cases, the impairment of two sinuses being described in 3.3-10.3% of the cases, and of three sinuses in 5.8-17.2%[3,6-8,11].

According to recent studies, FB represents 3.7% of all cases of inflammatory chronic rhinosinusitis (CRS) requiring surgery[9].

The pathogen most commonly implicated (in European countries) is Aspergillus (in 90-96% of the cases), especially Aspergillus fumigatus, rarely Aspergillus flavus, Aspergillus niger and Aspergillus nidulans. The Mucorales species are on the second place. Other fungal species are even more rarely detected: Cephalosporium, Candida albicans, Scedosporium apiospermum, Cladosporium[3,6,9,11].

The FB sinus pathophysiology remains unknown. The disorder develops in two conditions: penetration of hyphae and fungal spores into a paranasal sinus and creating the environment that contribute to the growth of fungi[9,12,13].

Three possible theories of FB development have been suggested: airborne, odontogenic and mixed. According to the airborne theory, large quantities of fungal spores in the air penetrate the sinuses through the natural ostia, multiply and become pathogenic when the sinus becomes an anaerobic environment. A possible cause may be the ostiomeatal obstruction, accentuated by anatomical factors (septum deviation, turbinate hypertrophy) contributing to the stasis occurred inside the sinuses, with the development of a hypoxic and anaerobic environment, with the lowering of the pH - a favourable and ideal condition for the proliferation of fungi and increasing the possibility of allergic reactions[9,12,13].

The odontogenic path is a iatrogenic one, where fungal colonization of the maxillary sinus occurs through a iatrogenic oro-antral communication, secondary to dental extraction, by periodontal lesions, channel perforation or, most frequently, after endodontic treatment with overfilling of the dental channel. The metals from the endodontic material, particularly zinc oxide, titanium, lead, calcium salts, barium and sulfur, accidentally introduced into the maxillary sinus during the endodontic treatment of the maxillary teeth, have a key role in the growth of fungi, the gradual filling of the sinuses and in the FRS pathogenesis. However, the odontogenic theory does not explain the FB occurrence in the ethmoid, sphenoid, frontal sinuses or in the maxillary sinuses of patients who have no history of dental pathology[9,12,13].

The mixed theory combines the features of the first two, being based on the ubiquitous nature of fungal spores, which can be inhaled and are present as saprophytes in the sinuses; but, under certain favourable conditions (ventilation disorders, foreign body), the fungal colony grows and causes sinusitis[13].

Recent studies suggest that immune disorders and factors affecting the nasal mucus may be more important in the FB pathophysiology than nasal anatomical variations obstructing the ostiomeatal complex. Events occurring in the rhinosinusal epithelium, including non-specific and specific immunity, require a more detailed description, because they allow an understanding of the pathophysiological mechanisms of FRS and are potential therapeutic targets[14].

The nasal immune system includes:

1. Superficial properties (mechanical, epithelial cell barrier, the physical characteristics of the mucus layer, mucociliary transport).
2. Innate or non-specific immunity: bactericidal activity in the mucus, proteins (lactoferrin, lysozyme, α2-macroglobulin, C-reactive protein), complement system, cellular immunity (activated polymorphic and phagocytic cells, including neutrophils, monocytes and macrophages).
3. Acquired or specific immunity: superficial immunoglobulins (Ig - IgA, IgM, IgE and IgG), macrophages, T and B lymphocytes, the mucosa-associated lymphoid tissue and localized at a distance (the adenoidian tissue, lymph nodes and the spleen)[15-17].

The mechanisms of defense of the non-specific immunity are mucociliary clearance (MCC), antimicrobial secretions and cells of the innate immune system[15,17].

The mucociliary apparatus has an important role in defending and maintaining the integrity of the airways and paranasal sinuses, in particular, and of the respiratory tract, in general. MCC drives the mucus and the particles trapped in the posterior mucus towards the walls of the nasopharynx, where these can be expectorated or ingested and subsequently digested by gastric juice. Mucociliary transport is the mechanism by which nasal cavities remove the secretions, inhaled particles, pathogens (bacteria, fungi, viruses) and other harmful substances. The major components of this system are the mucosa and the ciliated epithelial cells[17-19].

Physical and chemical changes of nasal epithelial cells, caused by the negative consequences of fungal, bacterial and viral toxins action and the inhalation of air pollutants, affect the epithelial physical barrier and mucociliary clearance, generates the worsening of the rheological properties of mucus, mucus stasis and synthesis of inflammatory mediators (histamine, bradykinin, prostaglandins and cytokines, developing a chronic inflammatory process. All these changes associated with ostiomeatal obstruction, enhanced or not by the anatomical factors, cre-

ate a hypoxic and anaerobic environment, by lowering the pH - a favourable and ideal condition for the proliferation and metabolism of fungi and increasing the possibility of allergic reactions[17,20].

The innate immunity involves a set of mechanisms of resistance, such as phagocytosis, which is not specific to a particular pathogen, while the acquired immunity presents a high degree of specificity, as the remarkable property of "memory". Despite these differences, innate and acquired immune responses relate and interact with each other, both of them being necessary for an effective immune protection[15,17].

The unspecific immune system cells are the lymphocytes (B and T), the phagocytic cells (dendritic cells, macrophages, neutrophils and eosinophils) and accessory cells (basophils and mast cells). These cells accumulate when the fungi interact with rhinosinusal epithelial cells and produce antibodies, cytokines (interleukins - IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α and interferons), chemokines, complement and various inflammatory mediators, which, in their turn, activate adaptive immunity. Interleukins (IL-4, IL-5, IL-9, IL-13) contribute to the secretion of IgE, are central mediators that play a key role in the chemotaxis, differentiation, activation and survival of eosinophils and promote independently eosinophilic inflammation with the development of FRS[15,17,20].

Together with the innate immune response, the acquired immune system contributes to chronic inflammation, observed in patients with CRS. T and B cells represent a major component of the acquired immunity. In the nasal mucosa and the paranasal sinuses, the B cells determine increased superficial levels of IgG_1, IgG_2, IgG_4, IgA, IgE and IgM[17].

IgE mediates the immediate hypersensitivity reactions, has an impact of hypersensitivity on the MCC function and it is proposed in the etiopathogeny of FRS, particularly of AFRS. This immunological mechanism suggests the role of fungal antigens in triggering IgE and IgG fungal-specific antibody synthesis in the blood (type I hypersensitivity and, probably, type III hypersensitivity) and eosinophilic inflammatory infiltration. Fungi and inflammatory mediators (IL-5, eotaxin) contribute to the degranulation of eosinophils and the release of large quantities of major basic protein. The latter possesses local toxic effects and favours epithelial lesions of the superficial mucosa[15,20].

Thus, the results of recent studies of FRS have contributed to the elaboration of the following hypothesis. Fungi on the sinus mucosa surface induce the production of cytokines that promote eosinophil migration through the epithelium towards the mucin. Eosinophils reach the mucin that contains fungi and releases high levels of cationic proteins (the major basic protein) to destroy fungi, favouring the appearance of epithelial lesions and aggravating the mucosal inflammation with the development of FRS[15,20,21].

The clinical picture in patients with FB is nonspecific, frequently identical with bacterial CRS resistant to antibiotic treatment. What should draw the clinician's attention are the unilateral symptoms: a sensation of chronic pressure or facial pain involving one of the paranasal sinuses, these being accompanied by possible associated symptoms (mucopurulent or purulent anterior-posterior rhinorrhea, nasal crusting, cacosmia or dysosmia). Occasionally, patients may present atypical symptoms – epistaxis, visual impairment, seizures, fever, cough and proptosis. In case of a sphenoidal localization of the FB, headache and facial pain are frequent. Symptoms are usually long lasting, may be present for months or even years, and FB can be detected occasionally. About 18% of patients may be asymptomatic and 10% present nasal polyposis[3,6,7,9,22,23].

Nasal endoscopic examination is nonspecific in most cases. Sinusoscopy, in case of maxillary localization, can highlight the characteristic appearance of "fungus ball" and allows us to harvest material for the fungal and histopathological analyses[6].

As a result of nonspecific symptoms, the imaging detection of this localized form of FRS is accidental[6]. Classical radiography may identify focal hyperdense areas, simulating a foreign body, that actually represent calcium phosphate deposits crowded in the areas of mycelium necrosis. Their unilateral localization is evocative[6].

The craniofacial CT scan is the examination of choice, the most reliable imaging method of diagnosis in the case of FRS, because it can provide information both about the characteristics and extent of lesion and for selecting the best surgical approaches. A heterogeneous, hyperdense sinus opacity, with microcalcifications or metallic appearance, partial or total, on the CT images, is very suggestive for the diagnosis and is observed in approximately 90% of the cases. The inflamed mucosa may be hypodense peripherally. In the case of CT examination, some signs or, rather, their association is evocative (but without being pathognomonic) for the fungal etiology:

- presence of an image of "metallic tone" intrasinusally, with the appearance of a foreign body;
- existence of multiple calcifications or microcalcifications on the sinus opacity side;
- heterogeneous content, unilateral or, rarely, in more sinuses;
- lack of osteolysis areas, possibly only a bone erosion, probably caused by the prolonged mechanical compression, exerted by the FB in the bony walls[3,6,7,9,22].

Nevertheless, the clinical sensitivity of the CT is about 62%, the specificity – 99%, the false positive rate – 22% and the false negative rate – 2%. The histopathological finding is the "gold standard" and the essential test to confirm a positive diagnosis of FB[11,14].

MRI is much less useful in cases of FRS, but it is indicated in complicated forms, with areas of osteolysis and expansion into adjacent tissues. The sinusal content ap-

pears on MRI as a hypointense or absent signal in T1 and T2 (pseudotumoral image), because of high protein density and dehydration of these caseous masses, with high concentrations of ferromagnetic elements[3,22].

The medical history, the clinical examination, the endoscopic examination and the imaging examination present valuable information only for the suspicion of FB; the definitive diagnosis relies on the macroscopic evaluation, biopsy and histopathologic examination of surgical pieces[6,9,24,25].

Anatomopathologically, FB is an accumulation of dense conglomerates of fungal hyphae that appear layer- or sphere-shaped disposed in the sinus cavity. The hyphae branch in a 45° angle and measure 3-6 micrometers in diameter, and the sporulating structures reach up to 30 micrometers. Important for the positive diagnosis of FB are the lack of fungal invasion in the sinus mucosa, blood vessels or bone, the lack of allergic mucin in the sinuses, the lack of granulomatous reaction, even if non-granulomatous chronic inflammation can be observed in the mucosa[3,6-8,22].

Direct mycological examination involves examining on the slide the caseous masses collected from the sinuses, visualizing under a microscope the mycelium filaments. The sensitivity of this examination can be comparable to the anatomopathological examination. In terms of sensitivity of the pathological examination, direct mycological examination has positive results in 62-94% of the cases[6-8,22].

Mycological cultures are less important in the case of FB because of the presence of fungi cultures in only 23-50% of the cases and the false positive results through inadvertent contamination, but also because of harmless omnipresent saprophytic spores in healthy persons[6,9,11,26].

The polymerase chain reaction is a molecular method that, by using the hybridization and sequence analysis, is more sensitive and reliable for the detection of fungi than standard culture methods. The method can be used to detect different species of viable and nonviable fungal pathogens in tissue samples obtained from the paranasal sinuses[26].

The positive diagnosis of FB in the paranasal sinuses is established on the basis of clinical and pathological criteria, suggested by deShazo:

1. Radiological evidence of sinus opacification with or without association of flocculent calcifications.
2. Mucopurulent material of the syrup type or clay material in one of the sinuses.
3. A matte, dense conglomeration of hyphae (the ball of FB), separated from the respiratory sinus mucosa.
4. Chronic inflammatory response of variable intensity in the mucosa adjacent to fungal elements.
5. The absence of histological evidence of fungal invasion of the mucosa, blood vessels or bone, visualized microscopically with staining for the fungi[11,23].

Complications are occasionally observed in the untreated FB. The most frequent is recurrent bacterial RS, which can be explained by fungal residues infection. The mucocele and pyocele, neurological complications (optic neuritis, ophthalmoplegia and seizures) are very rarely reported[11].

Differential diagnosis of FB is made with the invasive FRS, bacterial CRS, rhinoscleroma, sinus benign lesions (cyst, antrochoanal polyp, cholesterol granuloma, mucocele, hematoma, inflammatory pseudotumor), sinus benign tumors (sinonasal papilloma, fibrous bone lesion, salivary gland tumors, mesenchymal tumors - fibroma, lipoma, myxoma, etc.), sinus malignant tumors (carcinoma, adenocarcinoma, lymphoma)[25].

The goal of treatment in patients with FB is surgical removal of the fungal hyphae mass with restoration of the affected sinus drainage and ventilation. There are many controversies regarding the medical and surgical management of sinus FB. In most of the cases, the disorder is managed by endoscopic techniques[3,9,11,25]; open surgery (Caldwell-Luc), associated or not with endoscopic treatment, is required in a small number of cases, being determined by the impossibility of complete extraction of all the fungal concretions or foreign bodies by FESS[9,11,25]. Both techniques - endoscopic and open surgery - have similar results, but sinus endoscopic surgery is considered the "gold standard", a less invasive method and first-line surgical intervention, with a success rate of 97% and a negligible complication rate. The Caldwell-Luc procedure should be avoided because of the negative consequences for the sinuses physiology[9,25].

Both intraoperatively and postoperatively, it is essential to irrigate the sinuses with saline solutions, which increase MCC, facilitate the elimination of mucous secretions and the removal of any fungal residues. Also, intraoperatively, intrasinusal cortisone instillations may be used due to the anti-inflammatory effect. Since FB is a noninvasive form of FRS and the result of surgical treatment is, usually, excellent, local or systemic antifungal treatment is rarely required[11,24,27].

The prognosis of surgically treated patients with FB is very good. Cure rates are of 98-100%[8]. FB relapses are an exception, the overall relapse rate reported in the literature varying from 0% to 10% of the cases. The recurrence rate is low in endoscopic techniques (4-7%), and no relapses were reported in patients treated by the Caldwell-Luc procedure[11,22].

ALLERGIC FUNGAL RHINOSINUSITIS

Allergic fungal rhinosinusitis (AFRS) is a distinct and frequent form of FRS with the formation of nasal polyps, an immunologically-mediated noninvasive fungal inflammation, a chronic sinus disorder, with a marked propensity for recurrence. The disease is characterized by allergic fungal mucin accumulation in the paranasal sinuses,

type 1 hypersensitivity, characteristic histological picture and a propensity to form mucoceles and bone erosions[6,28-32].

AFRS is increasingly common especially in geographical areas with warm and humid climate, with a higher incidence in Southwestern United States, Sudan, North India and Saudi Arabia. AFRS affects adolescents and young adults aged between 20 and 42 years. Men and women are equally affected, although there are studies that have found this disorder to be more frequent in males. Generally, patients are from vulnerable socio-economic groups, usually immunocompetent and with a history of atopy, although not all of them have a history of allergic rhinitis or asthma. The incidence and real prevalence of AFRS is unknown. The overall incidence of the disease is estimated at 5-12% of all cases of sinus hypertrophic disorders requiring surgery[21,31-35].

The disease is considered an allergic reaction to the fungi. Causal fungi are usually from the dematiaceae family. Among these, Bipolaris spicifera is the most common species. Other types of fungi detected are Aspergillus, Alternaria, Curvularia, Exserohilum, Drechslera, Helminthosporium and Fusarium. Regional variations of the causative pathogen have also been described[5,31,32,33-35].

The physiopathology of AFRS remains unknown and controversial. The IgE-mediated allergy (type I hypersensitivity) and, possibly, the IgG-mediated one - immune complexes (type III hypersensitivity), according to Gell and Coombs classification, with subsequent triggering of an intense inflammatory response with eosinophils and tissue edema is considered an important pathophysiological factor in the development of AFRS. Tissue edema and other risk factors (septal anatomical changes or turbinate hypertrophy with obstruction of the sinus ostium) favours the stasis of secretions in the sinuses, which creates an ideal anaerobic environment for further proliferation of the fungi with increased degree of antigen exposure and possibility of onset of allergic reactions. At a certain time, the cycle becomes self-reinforcing, resulting in the occurrence of allergic mucin - the material that fills the sinuses involved in patients with AFRS. The lesion may extend to involve other sinuses, causing bone erosion[30,32,34,35].

The diagnosis of AFRS begins with a detailed anamnesis. There are some clinical aspects showing an alert sign for the clinician: patient age (usually young people, with the average age of 22 years), immunocompetent, with a long clinical picture of CRS[6,20,34,37]. During the clinical examination, nasal polyps are a universal endoscopic finding, but, in more severe cases, diplopia, ptosis and telecanthus may be identified[29,32,34].

Nasal secretions with a semisolid, thick, viscous consistency, of yellow-green, white-brown, gray, brown or black colour, of peanut butter consistency due to bacterial superinfection or fungal material, develop in the sinus cavities. This mass consisting of fungi and mucin is known as eosinophilic mucus or allergic fungal mucin. Eosinophils are the predominant and consistent cellular component of eosinophilic mucus[32,33-35].

The most important part of the diagnosis of AFRS is the histopathological examination. The histological evaluation of the biopsy or surgical specimen reveals the following triad: eosinophilia, Charcot-Leyden crystals and branching non-invasive fungal hyphae. Simultaneously with eosinophils, other inflammatory cells are also identified - plasma cells and lymphocytes[32-34]. Fungal cultures of the eosinophilic mucin can present some evidence to support the diagnosis and treatment of AFRS, but they must be interpreted with caution[34].

Other paraclinical investigations useful for the diagnostic of AFRS are the imaging techniques. CT images frequently present a dense, heterogeneous, asymmetrical material, filling one or more paranasal sinuses. Areas of heterogeneous intensity of the signal are present in the affected sinuses, a sign called the "double-density sign". They reflect the chelation of heavy metal salts (iron, manganese) and of calcium crystals, creating serpiginous areas of high attenuation, especially in the ethmoidal and maxillary sinuses. In more severe cases, by erosion of the adjacent bony walls, the disorder extends into the neighbouring tissues, including in the areas occupied by vital organs - brain, orbit and large vessels. Depending on the study, bone erosion frequency varies from 19% up to 98%[30-32,34,35].

The characteristic features of MRI are central hypointense areas or the lack of signal in T1/T2, with the increase of the peripheral signal T1 and T2[6,30-32,34].

Although several sets of diagnostic criteria of AFRS have been proposed, the most commonly used are the criteria recommended by Bent and Kuhn in 1994. For a positive diagnosis, patients must meet all five major criteria. Minor criteria only serve to support the diagnosis, to describe each patient individually[14,29,31,32,35].

Major diagnostic criteria of AFRS are: a) eosinophilic mucin without fungal invasion; b) positive staining for fungi of the sinus contents, without fungal invasion of the sinus mucosa; c) Nasal polyps with an incidence ranging from 75% to 100% of the cases; d) characteristic imaging signs; e) type I hypersensitivity to fungi (history, skin or serological tests)[14,31,32,35].

The other six criteria are minor: 1) a history of asthma; 2) unilateral predominance; 3) imaging evidence of bone erosion; 4) rhinosinusal positive fungal culture; 5) Charcot-Leyden crystals presence in the samples taken during surgery; 6) serum eosinophilia[6,30,31].

The main problem of the diagnosis is differentiating AFRS from other fungal diseases of the paranasal sinuses: local saprophytic colonization, FB, eosinophilic mucin RS, different forms of invasive FRS[6,34].

The optimal treatment of patients with AFRS is still not clear to date and there is no long-term successful treatment. The control of AFRS requires removal of se-

cretions to eliminate the antigen, restoring normal sinus drainage (surgical treatment) and the control of recurrences (medication). Combinations of surgical and medical approaches are used (corticosteroids, antifungal agents and immunotherapy) to manage complications of relieving symptoms. The goal of surgery is complete elimination of local secretions, allergic mucin and fungal residues, removal of nasal polyps, marsupialisation of the sinuses involved, preserving and maintaining the underlying mucosal integrity and the access for the postoperative treatment; it also aims at preventing subsequent long-term recurrence, either by immunomodulation (immunotherapy and/or corticosteroids) or antimicrobial fungistatic remedies. Sinus endoscopic surgery is necessary in most of the cases and is an important component of the management of AFRS[14,31,32,34,35].

Postoperative care begins immediately after surgery by nasal saline irrigation. Systemic corticosteroids, initiated before surgery, continue to be administered in the postoperative period. Corticosteroids administrated systemically or in the form of nasal sprays are the most effective agents in preventing recurrences and the selection of cases for the first-line treatment[14,29-31,35].

A better understanding of AFRS has led to some changes in the concept of management of this disease. Surgical treatment has evolved from radical interventions to more conservative processes with tissue preservation, being based almost completely on endoscopic techniques. Medical therapy has gone from systemic antifungal treatment to different forms of local and immunomodulatory treatment. Nowadays, the gold standard is considered endoscopic surgery combined with anti-inflammatory treatment[31,32,34].

Besides the potential complications of sinus surgery (risk of orbit injury and/or intracranial penetration), in the case of AFRS, there is an additional risk of damage to exposed structures (dura mater and orbit), because, the disease is often limited to these structures, without invading them[37]. The expansion of AFRS beyond the limits of the paranasal sinuses appears in the orbit or the anterior, middle and posterior cranial fossae[34,37].

AFRS is a non-invasive fungal, resistant, immunologically-mediated inflammation, with a marked propensity for recurrence. Surgery for AFRS without postoperative medical treatment is associated with recurrence rates of up to 100%. Overall rates of early (months) or late (years) recurrence ranges from 10% to 100%, with varying degrees of severity[30,32,34].

CONTROVERSES REGARDING FRS CAUSED BY EOSINOPHILS

FRS caused by eosinophils are a heterogeneous group of entities, including AFRS, eosinophilic mucin RS and eosinophilic FRS are distinct subcategories. These disorders are related, poorly differentiated syndromes, and they all refer to CRS accompanied by sinus opacification with allergic mucin or dense mucus thickening, of a colour ranging from light tan to brown or black[5].

Eosinophilic mucin RS was described by Ferguson in 2000 as a systemic disease disturbing the immunological control, associated with eosinophilia of the upper and lower airways and the lack of fungi in the eosinophilic mucin[2,38,39]. Unlike AFRS, where approximately 40% of the patients have asthma, in eosinophilic mucin RS over 90% of the patients have asthma. Eosinophilic mucin RS appears bilaterally and more frequently in older people, whereas AFRS may be unilateral and more common in younger people. There is no evidence of infection with Aspergillus in these patients, but the eosinophilic mucus is similar to that observed in AFRS. Eosinophilic mucin RS is similar to AFRS, but develops through other mechanisms. AFRS represents an allergic response to fungi in predisposed people, while eosinophilic mucin RS is caused by a systemic disorder of the immunological control. Total IgE levels are high in patients with both entities, but significantly higher in AFRS. Four mechanisms have been proposed for the pathogenesis of eosinophilic mucin RS: AFRS, non-allergic eosinophilic FRS, a superantigen inducing eosinophilic RS and aspirin-exacerbated eosinophilic RS[2,4,35,38,39].

Eosinophilic FRS. Unlike AFRS, which is an IgE-dependent condition, eosinophilic FRS is a non-IgE-dependent disease. In AFRS, there is allergic (eosinophilic) mucin with many eosinophils and the presence of non-invasive fungi with increased levels of fungal-specific IgE. Patients with eosinophilic mucin FRS and eosinophilic mucin RS do not show specific IgE and differ by the presence (eosinophilic FRS) or absence (eosinophilic mucin RS) of fungi visualized under the microscope in the eosinophilic mucin[4,38,39].

Diseases with eosinophilic mucin can be broadly divided into two categories – non-fungal and fungal. The non-fungal group includes eosinophilic mucin RS, and the fungal group includes AFRS and eosinophilic FRS with the presence of fungal hyphae[4,38].

AFRS, eosinophilic mucin RS and eosinophilic FRS could be different manifestations of the same pathological process, with considerable overlap of clinical features, imaging and immunological parameters, and the possibility of transition from one form to another in the same patient[2,4,36,38,39].

CONCLUSIONS

1. Non-invasive FRS includes FB and AFRS; generally, it does not invade the bone or tissues, but a longer history of the disease may eventually erode the bone (osteitis, osteomyelitis), resulting in the appearance of intracranial or intraorbital complications.

2. The diagnosis of FB is often delayed, because the symptoms are similar to those of bacterial CRS, disease progression is slow, oligosymptomatic and noninvasive. FB tends to occur in a single sinus, most often the maxillary sinus, and affected individuals are usually immunocompetent and non-atopic. The sinus contains hyperattenuated material and there may be evidence of chronic sinus disease or smooth bone erosions. Surgical removal is the main treatment, and recurrences are rare.

3. AFRS is more common in atopic young persons. Involvement of multiple sinuses is usually noticed. The condition is characterized by the presence of allergic mucin, Charcot-Leyden crystals and eosinophils. The radiological appearance is classic and considered one of the decisive arguments in the diagnosis of AFRS. The content of the sinuses tends to be hyperattenuated and the increased signal intensity on T1 images and low signal intensity on T2 images of the MRI are characteristic. Surgery and antiallergy medication are the mainstay of treatment, without the need for local or systemic antifungal toxic therapy.

Conflict of interest: The authors have no conflict of interest.

Contribution of authors: All authors have equally contributed to this work.

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