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Fungal rhinosinusitis: pathophysiology, diagnosis and treatment

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Abstract

Background: Fungal rhinosinusitis is a major clinical problem which should be considered in all patients and immunocompromised patients with chronic rhinosinusitis. It may be non-invasive or invasive with five main subtypes. Acute invasive fungal rhinosinusitis affects immunocompromised patients, usually with poorly controlled diabetes. Orbital and intracranial invasions are common, and mortality is high, except in cases of early detection and aggressive treatment. Chronic invasive fungal rhinosinusitis and chronic granulomatous fungal rhinosinusitis are characterized by a prolonged clinical course with slow progression of the disease, frequent invasion of the orbit and skull. Allergic fungal rhinosinusitis is a disease of young atopic individuals. There are usually involved all the sinuses with mucosa thinning and specific secretions. Fungus ball appears in one sinus, most frequently in the maxillary sinus, and affected individuals are not usually atopic. Anatomical and physiological interactions of the nose and paranasal sinuses form a dynamic system. Mucus is the first line of defense against inhaled irritants and pathogens. The hygiene of a normal airway is maintained by the mucociliary clearance. The immune system includes nasal epithelial surface properties, or non-specific innate immunity and specific acquired immunity.
Conclusions: The detailed knowledge of anatomical, histological and immunological properties of the nasal and sinus mucosa is essential for understanding the pathophysiology of sinus diseases, treatment planning and surgical approach in order to obtain a favorable result.
Key words: fungal rhinosinusitis, mycological examination, nasal mucociliary epithelium, immunology.

Introduction

Fungal rhinosinusitis (FRS) is a potentially dangerous condition, depending on the type developed and the opportunity for diagnosis. It is a highly controversial subject in today's medical world for the different research directions it offers [1, 2, 3].

In an attempt to elucidate the etiopathogenesis of rhinosinusitis (RS), several controversial hypotheses have been launched. A true "storm" among otorhinolaryngologists occurred in 1999 when Ponikau and Kern (Mayo Clinic, USA) launched the hypothesis that chronic rhinosinusitis (CRS) without nasal polyps has predominantly (in 93% of cases) a fungal etiology [1]. Despite the fact that until recently, bacteria have been considered responsible for CRS pathogenesis, the role of fungi is now recognized in the occurrence of certain forms of CRS. Fungal spores, by their ubiquitous nature, are always inhaled and stored in the respiratory tract mucosa. Although in healthy individuals in general, fungi have a saprophytic behavior, in some patients, under certain conditions, especially related to host immunity, fungi can induce diseases. FRS may include a wide variety of fungal infections that may vary in intensity, sometimes being lethal [2, 26].

Despite the recognition of FRS as a serious entity for more than two centuries and due to all studies carried out in recent years, the condition remains a controversial disease with evasive pathophysiology, incomplete knowledge about epidemiology and medical mycology. Further research is needed to elucidate the exact etiological and pathogenic role of fungal species in CRS, to improve FRS diagnosis and treatment in order to determine a better prognosis [1].

In recent years, the incidence of FRS has considerably increased due to patient's survival, contemporary diagnostic equipment and high frequency of conditions favoring fungal infections (diabetes mellitus, long-term pharmacological treatment with antibiotics, corticosteroids and immunosuppressants, radiotherapy, chemotherapy, immunodeficiency disorders). Fungal rhinosinusitis is classified into two main categories based on histopathological findings: invasive and non-invasive [1, 2, 3].

Epidemiology. Among patients with CRS, from 6% to 12% are found to have fungi in culture or at histopathological examination [40]. According to another study, 5-15% of all cases of CRS are considered RS of fungal etiology [41]. The incidence of fungal infections among patients operated for inflammatory rhinosinusitis accounts for 4.3% [43]. Globally, the FRS prevalence is about 900 million cases or 15% of the world's population [42].

In prospective studies, on large cohorts of patients with CRS (349-450 patients), FRS was diagnosed in 19.3-25.8% of cases. Approximately 10.3% of patients had allergic FRS (AFRS), 15.2% of patients - chronic FRS and 0.3% patients – fungus ball. Probably, the prevalence figures of different forms of FRS are underestimated because some patients with fungal diseases did not have clinical characteristics. This raised suspicions of FRS and therefore did not collect and send specimens for fungal analysis. In this case, the prevalence of non-invasive FRS may be higher [4, 5].

Etiology. The most common pathogens in FRS are Aspergillus (Fumigatus, Flavus and Niger), which represent 45% of all positive cultures, and *Mucormycosis,* but many other fungal species (Alternaria, Curvularia, Bipolaris, Candida etc.) are also reported. These fungal spores are omni-

present in the environment and can cause invasive and non-invasive conditions [2, 4, 5, 6, 26].

FRS pathophysiology remains unknown. In order to develop, fungal hyphae and spores must penetrate a paranasal sinus, and the conditions should contribute to the fungal growth. These conditions develop when some disorders disrupt normal mucociliary clearance (MCC) and / or obstruct sinus ostium [7]. The epithelial events, including specific and non-specific immunity, require a broader description because they allow understanding the physio-pathological mechanisms of FRS and are potential therapeutic targets [8]. In this context, we briefly recall the fundamental elements of rhinosinusal histology, immunology and physiology.

Notions of rhinosinusal histology. The internal plan of nasal pyramids consists of the nasal mucosa and the following types of epithelium:

1. Pseudostratified columnar epithelium (respiratory epithelium) composed of five major cell types: ciliary cells (columnar), non-ciliary cells (columnar), caliciform cells, basal cells (small polygonal stem cells – progenitor cells of other cell types); and small granular cells. This epithelium is found in the two posterior thirds of the nasal cavity.

2. Squamous and transitional epithelium (stratified epithelium containing cuboidal cells with microvilli) is found in the first third of the nasal cavity.

3. Epithelium of paranasal sinuses is a simple ciliary columnar type, with some caliciform cells and glands.

4. Olfactory epithelium in the olfactory area is a pseudostratified epithelium containing olfactory cells, basal cells and Bowman glands (small serous alveolar glands) [9, 10, 11].

The main glandular components of the lamina propria consist of serum glands, seromucous glands or Bowman glands. Seromucous glands and caliciform cells secrete acid glycoproteins (sialomucins and sulfomucins), while serum cells secrete neutral glycoproteins (fucomucin), enzymes (lysozyme, lactoferrin) and immunoglobulins [12].

The epithelial cells protect the upper and lower airways directly through MCC. The apical part of the ciliated cells, which accounts for about 80% of all epithelial cells, is covered by cilia (over 200 cilia per cell) whose apexes are located in the periciliary layer. The frequency of ciliary beats, a determining factor in the mucociliary transport rate, is between 10 and 20 Hz (800-1000 beats per minute) at normal body temperature, and the ciliary rhythm/beat consists of three phases: fast forward rhythm/beat (effective movement), during which the cilia expand to the maximum and are perpendicular to the cell surface, the tip being in contact with the mucus; the rest phase, in which the cilia are parallel to the cell surface and a slow return rhythm/beat (recovery rhythm/beat) [9, 10, 12, 13, 14].

The caliciform cells or mucus secreting cells produce an acid mucin in the amount of 0.1-0.3 mg/kg /day or 20-40 ml of mucus. The sufficient production of viscous, elastic and adhesive mucus is important in maintaining normal MCC. To prevent infections, mucus is weakly acidic, with a physiological pH value of 5.5-6.5 and has the capacity of a small chemical buffer [9, 10, 11, 12, 14].

An outpatient study of monitoring nasal pH for 24-hours showed neither a diurnal pH variation nor significant fluctuations in daily activities (ingestion of food and fluids, rest, sleep). The mean pH varied within the range of 5.97-7.85, while in the anterior part of the lower meatus the pH was higher than in the posterior part (7.1 versus 6.6) [15]. According to another study, the mean pH value in the nasal cavity was 6.3, while in the anterior part of the nasal cavity - 6.40 (from 5.17 to 8.13) and in the posterior part of the nasal cavity - 6.27 (from 5.20 to 8.00) [16]. In patients with CRS, the pH in the middle meatus is alkaline and is on average 7.81 ± 0.83, statistically significantly higher, compared to practically healthy subjects (7.35 ± 0.82, p = 0.00011) [17].

Both edema with the inflammation of the nasal mucosa and obstruction of sinus ostia may occur in the case of acid or alkaline nasal pH, resulting in ciliostasis – a cause known to develop CRS [18].

Therefore, the detailed knowledge of the mucosal histology of each nasal anatomical portion is essential to understand the pathophysiological mechanisms of nasal disorders and to plan the medical treatment and appropriate surgical intervention in order to obtain a favorable outcome.

Aspects of rhinosinusal physiology. The normal functioning of paranasal sinuses depends on three essential components that ensure a continuous secretion clearance: normal secretion, ciliary function integrity, and ostial patency [9, 10, 11, 13, 14].

There are two mechanisms that protect the respiratory system against several irritants, microorganisms and inhaled allergens – the nonspecific system (filtering function of the nose, nasal mucus with MCC and inflammatory reaction) and specific system (humoral and cellular immune responses) [11].

Assessment of MCC along with the use of rhino-scintigraphy and other objective and subjective methods in patients with CRS, with or without nasal polyps, treated medically and/or surgically, allows understanding of ciliary function and its role in CRS pathogenesis [19]. The ciliary function plays an important role in sinus clearance and prevention of chronic inflammation. Although knowledge of CRS has considerably increased, there are very limited data on predisposing factors for these conditions. The mucociliary transport speed is considered to be an important index of MCC function of the upper respiratory tract, an important mechanism for the protection of the respiratory ciliary epithelium [8].

The average speed of mucus flow and particle transport in healthy adults and in normal conditions is about 5-6 mm/min, ranging from 3 to 25 mm/min [9, 10]. Different factors may affect the ciliary function of epithelial cells. The MCC is reduced with age, being affected in the congenital abnormalities of the ciliary structure constitution (Kartagener triad, primary ciliary dyskinesia). The nasal mucosa dryness significantly affects the ciliary activity. At 50% relative humidity of inspired air, the ciliary motion stops after

8-10 minutes and at 30% relative humidity of inspired air – it stops after 3-5 minutes. The ciliary activity is optimal at 32-40°C. At 19-32°C temperature, the frequency of ciliary beat increases, at temperature above 40°C it decreases, and at temperature 7-12°C and above 45°C the ciliary activity ceases. Other factors, such as locally applied drugs, inhaled gases, exposure to large amounts of wood dust and chromium vapor, tobacco smoke, infections (viral, bacterial, fungal), chronic rhinosinusitis (allergic rhinitis, CRS, nasal polyps) can severely affect the ciliary function [9, 10, 12, 13, 14].

CRS causes significant changes in nasal mucosa, including secondary ciliary dysmorphology. These secondary changes may be reversible, but the time required to return to normal morphology depends on the severity of disorders, the persistence of the infection and other predisposing factors. Secondary ciliary dyskinesia and cytopathic epithelial changes play an important role in CRS pathophysiology [20].

Therefore, the anatomical and physiological interactions of the nose and paranasal sinuses form a dynamic system. Mucus forms a protective barrier to the airway epithelium; it is the first line of defense against the irritants and inhaled pathogens. The normal airway hygiene is maintained by MCC, the efficiency of which depends on the structure, number, movement, strength and coordination of cilia, quantity, composition and rheological properties of the periciliary layer and mucus layer, temperature. The unique rheological properties of mucus (viscosity, elasticity and adhesion) are significant determinants of these two protective mechanisms.

Rhinosinusal immunology. The nasal immune system includes:

1. Superficial properties (mechanical, epithelial, physical characteristics of the mucus layer, mucociliary transport).

2. Inborn or non-specific immunity (bactericidal activity of mucus, proteins – lactoferrin, lysozyme, α2-macroglobulin, C-reactive protein, complement system, cellular – polymorphic cells and activated phagocytes, including neutrophils, monocytes and macrophages).

3. Acquired or specific immunity (immunoglobulins – IgA, IgM, IgE and superficial IgG, informed macrophages, submucosal macrophages, IgM, IgG, T and B lymphocytes, mucosa-associated lymphoid tissue and remotely located (adenoids, lymph nodes and spleen) 11, 21, 22].

The 4 subclasses of IgG represent 75% of immunoglobulins found in the serum, with a concentration of about 10 mg/ml in healthy individuals. The least abundant immunoglobulin in serum is IgE, with a normal concentration of approximately 150 ng/ml [23].

The defense mechanisms of the innate immunity are MCC, antimicrobial secretions and cells of the innate immune system. The innate immunity involves a set of resistance mechanisms, such as phagocytosis, which is not specific to a particular pathogen, while adaptive immunity has a high degree of specificity, such as the remarkable "memory" property. In spite of these differences, the innate and adaptive immune responses are linked and interact with each other, and both are necessary for an effective immune protection [21, 22].

The immune system cells responsible for the reaction and release of soluble molecules are lymphocytes (B and T), phagocytic cells (dendritic cells, macrophages, neutrophils and eosinophils) and auxiliary cells (basophils and mast cells). The molecules released by these cells are antibodies, cytokines (interleukins - IL-1, IL-6, IL-8, IL-10, IL-12, TNF-α and interferons), chemokines, complement and various inflammatory mediators. There is evidence that IL-13 is a central mediator that independently promotes eosinophilic inflammation [21, 22].

IgA is a primary mucosa induced immunoglobulin; it is produced in humans more than any other class of immunoglobulins, and its major role lies in mucosal immunity. IgA can trigger cellular functions, such as degranulation and respiratory activation. Most people with IgA deficiency are not ill, IgA deficiency being associated with a large number of specific disorders: sinopulmonary, gastrointestinal, autoimmune and allergic diseases [21, 24].

The nose has two types of acquired cellular reactions as the first line of defense: IgA production, which forms insoluble complexes in mucus, and informed activated superficial immunological cells which are capable of phagocytosis. IgA is found in considerable amounts in nasal secretions [21, 24].

IgE is an immunoglobulin that causes allergic reactions and is mainly produced by lymphoid structures (tonsils and adenoids) and submucosa. IgE mediates immediate hypersensitivity reactions and has a hypersensitivity impact on MCC function [21, 24].

Thus, the nasal immune system includes superficial properties (mechanical, epithelial, physical characteristics of the mucus layer, mucociliary transport), innate or non-specific immunity (bactericidal activity of mucus, proteins, complement system, cellular immunity) and acquired or specific immunity (immunoglobulins, macrophages, T and B lymphocytes, lymphoid tissue).

Several predisposing factors for FRS (poor nutrition, low immunity, diabetes, long-term anti-TB treatment or antibiotics [25]) have been described, there are several possible pathophysiological pathways involving fungi in CRS and they can also act simultaneously or independently in a particular patient:

- Systemic or local IgE mediated reaction to fungi,
- Fulminant invasive infections – acute IFRS,
- Chronic invasive infections – chronic IFRS, chronic granulomatous IFRS,
- Epithelial lesions of superficial mucosa caused by eosinophilic proteases (major basic protein),
- Impairment of epithelial barrier with subsequent immunological reaction,
- Biofilms containing fungi [26, 27, 28, 29].

The mucin in patients with CRS contains heterogeneous eosinophilic clusters with high level of eosinophilic granules of major basic protein, a toxic cationic protein for extracellular microorganisms but also for the respiratory mucosa,

predisposing patients with CRS to secondary bacterial infections. Eosinophils can migrate into the respiratory mucosa by IL-13 expression, induced by adhesion molecules in the microvasculature, with subsequent migration from vessels to tissues. Another cytokine – IL-5, by inhibiting apoptosis, promotes the differentiation, activation and survival of eosinophils in tissues [26, 30].

Exposure of peripheral blood mononuclear cells to fungal antigens in vitro contributes to increased IL-5 and IL-13 production in 89% of patients with CRS. The increase in humoral response (serum IgG) correlates strongly with the increase in cellular response (IL-5 production). Less than 30% of patients with CRS have specific IgE antibodies to fungi [26, 30, 31].

These findings have led to a hypothesis in which fungi on the sinus mucosa surface could activate the immune system in sensitized patients and induce cytokine production, which promotes the migration of eosinophils through the epithelium to mucin. Eosinophils reach the mucin containing fungi and release cationic proteins to destroy fungi, thus they perpetuate and potentially aggravate the inflammation of the mucous membranes observed in CRS. Therefore, reducing the fungi in nasal and sinus cavities by antifungal treatment could reduce the immune and inflammatory responses in these clinically beneficial organisms of patients with CRS [26, 30].

Clinical trials with antifungal therapy for CRS, including CRS with nasal polyps, contributed to a symptomatic improvement, but did not demonstrate a substantial clinical effect [26, 32]. Some studies have found that antifungal treatment is safe and effective, reducing fungal antigenic load in nasal and paranasal cavities and then lowering the eosinophilic response. However, in order to determine the role of intranasal antifungal drugs in CRS treatment, controlled and blind studies are required [30, 32].

Thus, fungi are more frequently involved as an important pathogen in CRS etiology - they may play a minor role in CRS as part of a more complex multi-factor interaction, and conversely may be the main factor in some forms of CRS, however, fungi are not a universal etiological factor. However, the incidence and prevalence of various forms of FRS have not been accurately documented in prospective studies. It is crucial to estimate the exact physio-pathological mechanism in order to determine whether any changes in the treatment of CRS are needed and, if so, how to address them. In order to establish adequate and effective therapeutic strategies, and to minimize side effects, it is necessary to elucidate the pathophysiological mechanisms by which fungi initiate or perpetuate the inflammation, the nature of fungal interactions with the mucosal surface (e.g. as part of a biofilm or as a non-specific invader of disrupted epithelial barriers), optimal drug delivery methods [1, 4].The presence of fungi in the sinus mucosa does not explain the chronic inflammation in patients with CRS because they are only in the mucus and histologically do not invade the tissues. Since IgE antibodies to fungi have been detected in less than 50% of patients, type I hypersensitivity reaction in fungi does not fully explain the pathological process. Therefore, CRS could be caused by an immunological response to fungi in nasal and sinus cavities of patients with CRS, but not necessarily type I hypersensitivity reaction [32].

Fungal infections of paranasal sinuses can manifest as two distinct entities. The most severe (invasive) infections occur in patients with a compromised immunity (malignancies, autoimmune diseases, malnutrition, HIV infection, diabetes mellitus or immunosuppressive therapy) and are relatively easy to recognize by symptomatology and fulminant progression. The mortality rate is quite high in IFRS, early diagnosis and appropriate treatments are vital [33].

Non-invasive infections are chronic and, unfortunately, are often confused and treated as bacterial CRS for long periods of time, until the disease is exactly diagnosed [1, 33].

Clinical picture. FRS can often be difficult to diagnose, since its symptoms may be easily confused with the symptoms of bacterial CRS. The most common symptoms are pressure and /or numbness in the face area, frequent nasal congestion, inflammation of sinuses, nasal polyps, frequent sneezing, cough, headache, facial pain [6].

The clinical picture of invasive infections involves the presence of a viscous dark secretion in sinus cavities, spreading into adjacent tissues – orbit and intracranial structures [6].

FRS classification. To be able to predict patient's prognosis and response to treatment, a FRS classification is needed. It is important to make a distinction between invasive and non-invasive forms of FRS. All attempts to systematize FRS confirm that there is no single opinion concerning FRS so far, but fungi are definitely involved in its etiopathogenesis, and its incidence and prevalence are much higher than previously thought [1, 26].

Currently, most rhinologists acknowledge the following clinical and pathological forms of FRS:

1. *Non-invasive FRS (absence of mucosal layer invasion):*
- Local colonization with saprophytic fungi
- Fungus ball
- FRS caused by eosinophils (AFRS, eosinophilic FRS, eosinophilic mucin RS).

2. IFRS (*with mucous layer invasion*):
- Acute (fulminant) IFRS,
- Chronic IFRS,
- Chronic granulomatous (indolent) IFRS [2, 33, 34, 35].

Therefore, there is invasive and non-invasive FRS. Acute FRS includes acute IFRS (fulminant), and chronic FRS - chronic IFRS, chronic granulomatous IFRS, fungus ball, AFRS. FRS forms are distinct entities with different clinical, laboratory and radiological characteristics. Each FRS form can be differentiated and has different treatment and prognosis approaches.

General criteria for diagnosing different types of FRS. The most important step in FRS management is correct diagnosis, based on solid criteria, which will lead to a better prognosis of this condition. Due to potential invasiveness, especially in patients at risk, a correct and rapid diagnosis of FRS is essential in order to initiate the treatment as early as

possible and to ensure a favorable prognosis. FRS diagnosis should be based on clinical examination and paraclinical investigations, the most important of which is histopathological evidence of fungi presence [1].

Two essential conditions are required for FRS diagnosis: RS diagnosis (the ubiquitous nature of fungi should not be forgotten) and evidence of fungal infection. The latter can be confirmed by histopathological and/or mycological examination. Histopathology, according to some literature data, is still the standard method ensuring the best sensitivity in the detection of rhinosinusal fungal infection. Mycological examination is a useful tool and has a certain value, but it involves special conditions for harvesting, transporting and processing in order to obtain positive results. Correct sample harvesting and transporting are essential for the precise identification of fungi [1].

The diagnosis of FRS begins with a detailed anamnesis. Often, patients have a history of rhinosinusitis for prolonged periods of time or rhinosinusitis refractory to medical or surgical treatment for bacterial CRS [1, 25].

Histopathological (anatomopathological) examination is a quick and relatively inexpensive technique that often confirms the positive diagnosis or, at least, induces a suspicion of diagnosis. It detects the presence of fungi and confirms the tissue invasion. In addition, some histopathological parameters in CRS are predictive of the favorable response to functional endoscopic sinus surgery [1, 36, 37]. The histopathological examination for the detection of fungi reveals inflammatory cells in tissues and mucus, as well as the existence of specific reactions (Charcot-Leyden crystals). Staining can be done using hematoxylin-eosin, periodic Schiff acid or Grocott-Gomori silver hexamine impregnation, the latter can also identify fungal morphology [1]. However, some fungi (Aspergillus and Mucorales) have a similar morphology, making it difficult to distinguish between them by Grocott-Gomori silver hexamine stain. Immunohistochemical staining MUC5B is a much more sensitive method for the detection and identification of fungi in FRS, especially differentiating Aspergillus species from Mucorales species [44].

Mycological examination is also an essential step in the analysis and can be done with or without staining. The poor sensitivity of fungal sinus culture techniques with significant false-negative rates makes difficult the determination of the exact FRS incidence and prevalence [4]. The fungal detection rates using the culture method vary greatly – from 6% to 93% [43, 45]. Since fungi cultures are frequently negative, Bent and Kuhn have accepted that if all the other diagnostic criteria exist, including the positive histopathological examination of the sinus mucin, positive fungal culture is not required to confirm the diagnosis [38].

The usefulness of immunofluorescence techniques in the diagnosis of fungal infections has been confirmed in many studies. They can be used to early detect and identify fungi on different cultures or almost any biological product (blood, urine, cerebrospinal fluid, etc.) [1].

To diagnose fungal infections, there are some other techniques using the immunoassay (ELISA) to determine active antigens or genomic amplification by molecular biology techniques (polymerase chain reaction – PCR) [1].

The serological test aims at identifying specific immunoglobulins that are a marker of early or present fungal infection. It is noteworthy that two essential conditions are required to determine specific serum IgG: long enough contact of the fungal antigen with the host immune system and competent host immune system. This explains why the serological test is negative in localized fungal infection of fungus ball and in immunosuppressed patients (AIDS, leukemia, etc.) [1].

Skin tests are very important diagnostic tools in the case of allergic fungal disease. Lately, skin prick tests have become a norm, standardizing fungal extracts for classical intradermal tests [1].

Unfortunately, we have no standard criteria for imaging diagnosis of FRS. CT scan is the most useful imaging method, due to an increased sensitivity and ability to identify signs at early stages, but with reduced specificity for this condition. CT is performed at a 3 mm interval in the axial and coronal planes, using both bone and tissue windows. Magnetic Resonance Imaging (MRI) has a limited value for RSF diagnosis, being a starting point for the diagnosis of these clinical entities. It is often required in order to double the CT examination [1].

Several suspicions about FRS diagnosis are described:

- Isolated damage to a paranasal sinus (maxillary, sphenoid) or asymmetric disorders (significant percentage of unilateral damage) with opacification and calcification inside and / or different density on CT scans, hyposignal in secretion and hypersignal in the mucosa injured on T2 sections of MRI.
- Exacerbated facial pain, signs and symptoms non-specific to RS (nasal congestion, headache, rhinorrhea, etc.), nasal and facial edema.
- Severe thick brownish (mucin) and / or caseous secretion during endoscopic diagnosis or during surgery.
- Ischemic or necrotic areas on endoscopic or surgical examination.
- Direct examination of secretions with degranulated and / or necrotic eosinophils (Charcot-Leyden crystals).
- Direct identification of hyphae, if positive culture is negative, if both are negative – positive PCR (considering the clinical and radiological data described above).
- Mucosa with non-specific inflammation, if the fungus is present in the epithelium, submucosa and / or bone - invasive presentation (correlates with the clinical characteristics, findings and patient`s immune status).
- Clinical and radiological presentation similar to eosinophilic mucin; there are no available methods for positive fungal identification, which may indicate non-fungal eosinophilic CRS (mucinic, atopic or non-atopic).
- The presence of fungi on direct examination by cul-

ture harvesting and / or PCR can also be determined in normal subjects [35].

The diagnosis of FRS is primarily histological. The distinction between IFRS and non-invasive FRS is based on histopathological evidence of fungal invasion of the sinus and bone mucosa and, eventually, spread to the adjacent structures and tissues (orbit, anterior skull base and pterygopalatine fossa). In non-invasive FRS, fungal infection is limited to the sinus cavity without fungal invasion of the mucous membrane and bones [6].

Non-invasive FRS includes fungus ball and AFRS, which generally do not invade bone or tissues and, more commonly, are a result of skin hypersensitivity reactions. But a long-term development of the disorder may eventually erode the bone (osteitis, osteomyelitis) that may cause an intracranial or intraorbital complication. Complications may occur in an immunocompetent patient and are characterized by the presence of allergic mucin, Charcot-Leyden crystals, eosinophils and other inflammatory cells [6, 25, 34].

The diagnosis of fungus ball is often delayed because the symptoms are generally similar to those of bacterial CRS, the course of the disease is slow, oligosymptomatic and non-invasive. At the same time, fungus ball tends to appear in a single sinus, unilaterally, most often in the maxillary sinus, usually the affected individuals being non-atopic. The sinus contains hyper attenuated material and there may be evidence of chronic sinus disease or smooth bone erosion. Surgical removal is the basic treatment, recurrences being unusual [34].

AFRS is more common in young atopic people. Pansinusitis is usually found with expansion and thinning of the affected sinuses. The disease is characterized by the presence of allergic mucin, Charcot-Leyden crystals and eosinophils [6, 25, 34, 46]. The sinus content is hyper attenuated with high signal intensity on MRI images T1 and low signal intensity on MRI images T2. Surgical extirpation and antiallergic remedies are the basis of the treatment, the systemic or local antifungal toxic therapy not being necessary [34].

IFRS is a more fatal condition, defined by the presence of fungal hyphae in the mucosa, submucosa, bones or blood vessels of paranasal sinuses with orbital and intracranial extension. These subtypes are distinct entities with different clinical and radiological characteristics, with different treatment and prognosis strategies, which predominantly occur in immunocompromised patients in about 50% of cases. According to some studies, IFRS incidence is 0.5-4% of patients with bone marrow transplant. The imaging features are often subtle at the initial stages, and sinus evaluation in these patients is performed to determine early invasion signs. The mortality rate tends to be high, except the cases of early detection and aggressive treatment. In patients with untreated IFRS the mortality is significant and may reach 85-100% [3, 25, 34, 35, 39].

The risk factors for RSFI development include the use of antibiotics for prolonged periods of time, permanent sinonasal catheter, prolonged nasal intubation, immunosuppressive medications, metabolic or steroid abnormalities, poorly controlled diabetes, long neutropenia, and sinus disease [3].

The acute forms of IFRS progress rapidly within hours or days to fulminant intracranial infections. The chronic forms show slow growth and cause slow tissue destruction with subsequent invasion. Disease duration of less than 4 weeks differentiates acute form from chronic one. The term "subacute IFRS" can be used in rare situations – in patients with disease duration within 1-3 months [25, 34, 39, 42].

Chronic IFRS and chronic granulomatous IFRS are characterized by a long-lasting clinical development (more than 3 months) with slow progression of the disease, orbital complications and intracranial complications. Imaging manifestations can mimic agressive neoplastic lesions [34, 42].

FRS complications range from relatively benign to potentially lethal and are divided into three categories:

- Local - mucocele of paranasal sinuses, frontal bone osteomyelitis, subperiosteal abscess of the frontal bone,
- Orbital - inflammatory edema, orbital (post septal) cellulitis, subperiosteal abscess, orbital abscess, cavernous sinus thrombosis,
- Intracranial - meningitis, epidural abscess, subdural abscess, intracerebral abscess, cavernous sinus thrombosis, upper sagittal sinus thrombosis [25].

The intracranial, insidious and rapid extension is the most feared complication of IFRS with high mortality rates. The following forms of extension are known: 1) direct – the most common, 2) haematogenic – dangerous and asymptomatic with emboli and mycotic thrombus formation, 3) perineural with the cranial nerves paralysis and extension to the base of the anterior skull, 4) through the cribriform plate of the ethmoid bone at the base of the anterior skull, 5) very rarely by surgery or blood transfusion [25].

Therefore, the most appropriate approach is early diagnosis and intervention. With the current available diagnostic means (CT, MRI, microscopic examination, cultures and nasal endoscopy), diagnosis is much simpler, however, a high degree of clinical suspicion is required. The treatment results have greatly improved with advances in medical and surgical technology. New antifungal agents and other remedies have greatly contributed to better results through increased efficacy and minimized toxic side effects of traditional medicines [25].

FRS management is divided into two main directions: surgical treatment - which is aimed at eliminating fungal antigen and is most commonly the main treatment and conservative treatment – which seeks to prevent relapses, but has not been standardized so far and there is no clear evidence of the efficacy of any of the therapeutic agents used. Functional endoscopic sinus surgery is used together with long-term conservative treatment, oral and intranasal glucocorticosteroids, immunotherapy, antifungal medication and antimicrobial agents [25].

Functional endoscopic sinus surgery is the main option. There are various surgical methods in FRS. In the case of non-invasive and invasive disease, which is limited to sinuses without obvious dural involvement or osteomyelitis,

endoscopic elimination is the method of choice. If there is FRS extension, particularly intracranial extension, non-endoscopic approaches with the involvement of neurosurgeons team are considered [25].

In fungus ball, surgery always resolves the disease without the need for further pharmacological treatment. In AFRS, surgical treatment improves the symptoms of nasal respiratory obstruction, but local drug therapy is necessary. With the help of medical treatment, surgery resolves chronic IFRS and prevents the intracranial spread of complications. In patients with acute (fulminant) IFRS, timely surgical treatment prevents the onset of intracranial complications and makes the antimycotic polychemotherapeutic treatment possible in order to control the disease [43, 47].

The main pillar of the medical treatment of FRS is the administration of antifungal preparations: Amphotericin B at a maximum dose of 2-4 g/day, Lipozomal Ampho B at a dose of 4 mg / kg / day and can be increased to 10-15 mg / kg / day, fluconazole or itraconazole 400 mg twice daily [25].

Postoperative treatment includes regular endoscopic examination and follow-up, nasal lavage twice daily with Amphotericin B. Antifungal preparations are continued for approximately 4 weeks or until complete recovery confirmed by endoscopic examination [25].

Conclusions

FRS is one of the most challenging diseases for otorhinolaryngologists, primarily in terms of diagnosis and treatment. Because of the lack of standard diagnostic criteria and the potential FRS invasiveness, especially in at-risk patients, it is essential to have a correct and rapid diagnosis in order to initiate treatment as quickly as possible to get a favorable prognosis. The only way to establish a reliable diagnosis is to perform a detailed clinical examination and biopsy sampling [1].

FRS is an important clinical issue with various manifestations that should be considered in all immunocompromised patients and in all patients with CRS. It may be invasive or non-invasive, with five main subtypes [34].

Acute IFRS affects immunocompromised patients and patients with poorly controlled diabetes. The orbital and intracranial invasion is common, and mortality is high, except in cases of early detection and aggressive treatment. The imaging features are subtle at the initial stages and require attention to detect early signs of invasion [34].

Chronic IFRS and chronic granulomatous IFRS are characterized by a prolonged clinical development, slow progression of the disease, orbital and cranial invasion. Imaging manifestations can mimic aggressive neoplastic lesions [34].

AFRS is a disease of young atopic individuals. There is usually pansinusitis expansion and thinning of the affected sinuses. The contents of sinuses are hyper attenuated, with an increased signal intensity of T1 and a low signal intensity of T2 on MRI images. Surgical removal and antiallergic treatment are the main management methods, systemic or local antifungal toxic treatment not being necessary [34].

Fungus ball occurs in a single, unilateral sinus, most commonly in the maxillary sinus, and the affected individuals are usually not atopic. Sinuses contain hyper attenuated material and there may be evidence of chronic rhinosinusitis or smooth bone erosion. Surgical removal is the method of choice, the recurrence being unusual [34].

Therefore, understanding the different types of FRS and their special radiological characteristics allows diagnosing and initiation of the early treatment to avoid a delayed outcome, complications or fatal outcomes.

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