LITERATURE REVIEW

Difficulties in the diagnosis of fungal rhinosinusitis – Literature review

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ABSTRACT

Fungal rhinosinusitis is an important pathological entity, a highly controversial topic in the medical world today, by the various research directions it offers. In order to be able to predict a patient's prognosis and his response to treatment, first we must have a classification of fungal rhinosinusitis. The authors considered it is important to make a distinction between invasive and noninvasive forms of fungal rhinosinusitis. The most important step in the management of fungal rhinosinusitis is to have a correct diagnosis, based on strong criteria, which will lead to a better prognosis of this disease. Because of its invasiveness potential, especially in patients at risk, it is essential to have a correct and fast diagnosis in case of fungal rhinosinusitis, in order to begin the treatment as fast as possible, for a favourable prognosis. The only way to establish diagnosis in a reliable way is to make a detailed clinical examination and to take biopsy samples.

KEYWORDS: fungal rhinosinusitis, mycological examination, fungus ball, allergy, invasive

INTRODUCTION

Fungal rhinosinusitis is an important pathological entity, a highly controversial topic in the medical world today, by the various research directions it offers. Rhinosinusitis, in general, is one of the most frequent management health problems worldwide[1]. The economic burden this condition achieves is huge[2]. One of the explanations for elevated social and financial efforts could be that, by now, the etiopathology mechanism of these chronic diseases is not yet fully elucidated, and thus there is still no causal therapy which has been proven to be undeniable by controlled trials[3].

In an attempt to elucidate the etiopathogeny of rhinosinusitis, several controversies were launched. A veritable "storm" in the world of Otolaryngology appeared in 1999, when Ponikau and Kern (Mayo Clinic, USA) launched a hypothesis which supposed that chronic rhinosinusitis (CRS) without nasal polyps have, mostly, fungal etiology[4]. Although, until not long ago, bacteria were considered responsible for the pathogenesis of CRS, the role of fungi is now recognized in the occurrence of certain forms of CRS. Fungal spores, through their ubiquitous nature, are continuously inhaled and stored in the respiratory tract mucosa. Although healthy individuals generally have saprophytic behaviour, in some patients, under certain conditions, related especially to the host defence, fungi may induce diseases. Fungal rhinosinusitis may include a large diversity of fungal infections that can vary in intensity, sometimes being even lethal[5]. The most frequently involved pathogen agents are *Aspergillus* species, but many other fungi species are also reported.

In order to be able to predict a patient's prognosis and his response to treatment, first we must have a classification of fungal rhinosinusitis. The authors considered it is important to make a distinction between invasive and noninvasive forms of fungal rhinosinusitis. Nowadays, the general consensus of classification is in: invasive forms (with three subtypes: acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis and granulomatous invasive fungal rhinosinusitis) and non-invasive forms (fungus ball, allergic fungal rhinosinusitis)[6-10]. All these attempts to systematize this disease that were made over time indicate that, so far, there is no unified vision

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regarding these pathological entities, but it is sure that in chronic rhinosinusitis etiopathogeny, fungal involvement is a certainty, and these diseases are much more common than previously thought.

Diagnosis of fungal rhinosinusitis is sometimes complicated and it should be based on clinical examination and paraclinical investigation, of which the most important is the histopathological proof of fungi presence.

The treatment of fungal rhinosinusitis is divided into two main sections: surgery - which aims to remove the fungal antigen and is, most frequently, the main treatment, or medical treatment - which attempts to prevent relapses, but it has not been standardized so far; there is no clear evidence of efficacy for any of the therapeutic agents used. Endoscopic sinus surgery is used along with long-term medical treatment, oral and intranasal glucocorticosteroids, immunotherapy, antifungal medication and antimicrobial agents to control the issue[11].

GENERAL DIAGNOSIS CRITERIA IN VARIOUS TYPES OF FUNGAL RHINOSINUSITIS

Diagnosis in case of fungal infections of the nose and paranasal sinuses, in general, can be achieved directly or indirectly. Direct diagnosis aims to isolate and identify the fungus. Sampling is essential for accurate identification of fungi, with some basic sampling principles[4,12]: sterile tests and accurate sampling; it is important to take samples from the periphery of the fungal lesion, using sterile swabs. Also, it is important to transport samples to suitable temperatures and to the appropriate media for the examination required (formalin-fixed and humidified, Bouillon environment).

Pathological examination carries on tissues and the mucus, for the search of fungal agents, inflammatory cells and the existence of specific reactions (e.g. Charcot-Leyden crystals). Staining can be made using: hematoxylin-eosin (HE), periodic acid-Schiff (PAS) or Gomori silver impregnation that can distinguish between the morphology.

Histopathological examinations (Figure 1) are also fast and relatively inexpensive techniques which often bring positive diagnosis or, at least, raise the suspicion of diagnosis. It makes it possible to detect the presence of fungi and to confirm tissue invasion (extremely important in diagnosing opportunistic fungal infections).

Mycological examination is also an essential step in the analysis and it may be performed with or without coloration. Its sensitivity should be similar to histopathologic examination. The Mayo Clinic team proposed an original method of harvesting and processing the mucus from the middle meatus or ethmoid, if there is suspicion of allergic fungal rhinosinusitis and tracking crop at 2, 5, 7, 10 and 30 days. In other words, an insufficient pursuit for a period of time can determine false-negative results[4].

The utility of immunofluorescence techniques in the diagnosis of fungal infections was strongly confirmed by many studies. They can be used for the early detection and identification of fungi on different culture media or almost any kind of biological products (blood, urine, CSF, etc.).

For the diagnosis of fungal infections, there are also other techniques that can be used: an immunoassay (ELISA) to determine antigens assets, a genomic amplification by techniques of molecular biology (PCR).

Serological examination aims to identify specific immunoglobulins that represent a marker of earlier or present fungal infection. It should be noted that, in order to notice specific serum IgG, two essential conditions are necessary: the fungal antigen must have a long enough contact with the host immune system and the host immune system must be competent. This explains why, in case of localized fungal sinus infections ("fungus ball") in immunosuppressed patients (AIDS, leukemia, etc.), serology is negative.

Skin tests are very important diagnostic tools in case of allergic fungal pathology[12]. Lately, skin prick tests have become a standard, the standardized fungal extract, for classical intradermal tests.

1. Fungus Ball

The fungus ball (mycetoma) is a form of localized noninvasive fungal rhinosinusitis, non- or less-aggressive, extramucosal, and, in particular, it occurs in immunocompetent patients. The most frequently involved pathogens in the European countries are Aspergillus, mainly Aspergillus fumigatus. Also, we can encounter other species of Aspergillus or other fungi, as follows: Aspergillus flavus, Niger and, less often, Cephalosporium nidulans, Candida albicans, Scedosporium apiospermum, Mucorales, Cladosporium, etc.[13-15].

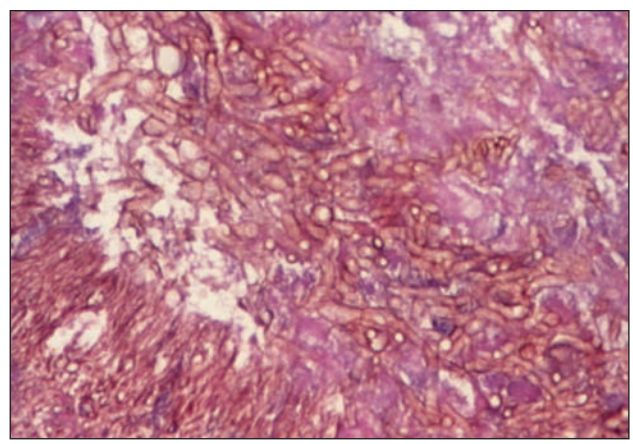

Figure 1 Histopathological examination – Aspergillus (HE coloration, 20x)

In terms of clinical diagnosis, patients usually present with nonspecific symptoms of chronic rhinosinusitis and they only have one sinus cavity involved. Generally, they are less symptomatic, the disease being recurrent and resistant to proper antibiotic treatment. What should call attention to the clinician are the unilateral symptoms, accompanied by eventual pain, with possible associated symptoms: purulent rhinorrhea, nasal crusting, or dysosmia/cacosmia. In the cases when the fungus ball is localized in the sphenoid sinus, headache or facial pain is frequently encountered.

The nasal endoscopy is non-specific in most of the cases. When maxillary sinuses are involved, it is helpful to perform a sinusoscopy that may reveal a characteristic "fungus ball" (Figure 2), which allows us also to collect material for the histopathological analysis.

When it comes to interpreting the results of a maxillary sinus puncture, the clinicians should pay great attention because, due to the increased consistency of mycological material, one may encounter false-negative results, which could determine diagnostic errors. Because the symptoms are usually non-specific, this form of localized fungal rhinosinusitis is randomly discovered. Although it is not yet out of the common use, classic radiologic examination can identify hyperdense focal areas, simulating a foreign body, which are actually calcium phosphate deposits agglomerated at the site of mycelia[16, 17]; the unilateral localization is evocative.

Rhinosinusal computed tomography represents the most reliable diagnostic imaging method for fungal rhinosinusitis in case of localized forms. In case of CT images, there are some evocative, but not pathognomonic signs that may indicate fungal etiology[18-24]:

- presence of an image of "metallic tone" intrasinusally, looking like a foreign body;
- existence of multiple calcifications or metallic densities, areas of microcalcification;
- heterogeneous content, unilateral or, more rarely, across multiple sinuses;
- lack of areas of osteolysis or bone thinning, probably only possible because of the pressure exerted by the long fungus ball on the bony walls.

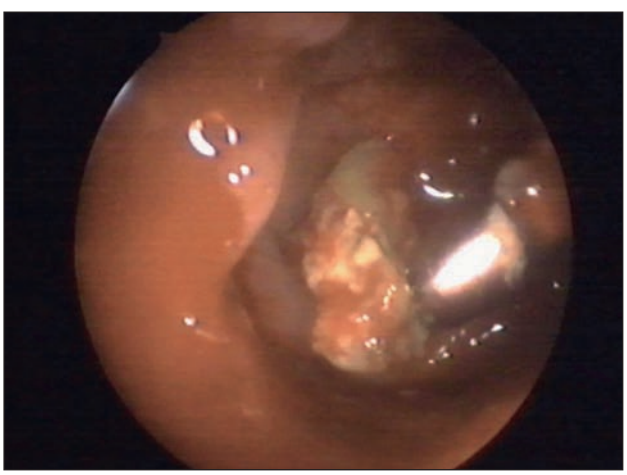

Figure 2 Maxillary fungus ball – intraoperatory image

MRI is much less useful in cases of fungal rhinosinusitis, but it is indicated in complicated forms, with areas of osteolysis and extension to adjacent tissues. The content appears on MRI as a hyposignal or no signal in T1 and T2 (pseudo MRI image)[25-28].

Nasal endoscopy or imaging tests may lead to a diagnosis of suspicion of fungus ball, but the only ones that establish the diagnosis of certainty are histopathological and mycological examinations. Pathological examination should be analyzing both fragments from fungal material and sinus mucosa, using special stains (PAS, Grocott-Gomori) to observe mycelial filaments and, more rarely, to identify the morphology of the fungi. In order to have a positive diagnosis of the fungus ball, we must notice any invasion of the sinusal mucosa by fungi. In terms of sensitivity of the pathological examination, the direct mycological examination seems to have a positive result in 62-94% of cases[13, 14, 27, 28]. The sensitivity of direct mycological examination is good, being comparable to the pathological examination[29-31]. Mycological cultures are less important for fungus ball diagnosis, due to false positives that may appear because of accidental contamination or it may identify only ubiquitous spores, without pathological significance in healthy individuals[32]. Also, the cultures of lavage, after the proposed technique of Ponikau et al.[4] are of little interest for the fungus ball diagnosis due to strict locality sinus[42].

2. Allergic Fungal Rhinosinusitis

Probably one of the most controversial affections in rhinology, allergic fungal rhinosinusitis (AFRS) was first described in 1983 by Katzenstein[33], who called these entities "allergic Aspergillus sinusitis" and also noted their similarities with broncho-pulmonary allergic aspergillosis (ABPA). 2 decades after this first description, many uncertainties still remain regarding the definition and pathophysiology of AFS. AFRS is characterized by the existence of allergic fungal mucin that has a thick aspect with a high concentration in eosinophils secretion and characteristic histologic images.

In 1994, based on the clinical characteristics of a group of 15 patients, Bent and Kuhn proposed 5 criteria for the diagnosis of AFRS[34]. In order to have a positive diagnosis, patients must fulfil all major criteria. Minor criteria have only the role of supporting the diagnosis, to describe individual patients.

The major diagnostic criteria are:

1. The presence of type I hypersensitivity, confirmed by history, skin tests and serology

2. The presence of nasal polyposis
3. Characteristic signs (hyperattenuation areas) in the computer tomography examination
4. The presence of eosinophilic mucin, without sinus tissue fungal invasion
5. Histopathology or positive cultures for fungi in sinus contents, taken during surgery.

Minor criteria are represented by the presence of asthma in the past, unilateral localization of the illness, imaging proof of bone erosion, positive cultures for fungi, presence of Charcot-Leyden crystals in samples prelevated during surgery, serum eosinophilia.

Due to the fact that all patients with AFRS met the criteria for chronic rhinosinusitis proposed by DeShazo and Swain, Ponikau suggests that the term AFRS (indicating a IgE-mediated response), is replaced by the term "eosinophilic fungal rhinosinusitis" (EFS) and the term of allergic mucin is replaced by the term "eosinophilic mucin"[4].

For simplicity, most authors think that, in order to put a diagnosis of AFRS, the presence of the following criteria is sufficient: (1) identify the presence of fungal hyphae, (2) presence of eosinophilic mucin, without causing tissue invasion and (3) proof of the host fungal allergy. Eosinophilic mucin, cornerstone of AFRS diagnosis, is established only from the histological perspective, based on the existence of the fungal elements (hyphae), non-invasive, diffusely distributed among Charcot-Leyden crystals (lysophospholipase)[4,6,35-39].

Diagnosis begins with a detailed anamnesis. Usually, patients have a history of rhinosinusal affection that was refractory to medical or surgical treatment, used in case of bacterial rhinosinusitis[40].

There are some clinical aspects that may represent an alert sign for the clinician, like the age of the patient (usually young, with a mean age of 22), he is immunocompetent, has unilateral affection of the nose and paranasal sinuses, presence of atopy in the past and presence of nasal polyposis. Nasal secretions have a green-black rubbery colour and they are formed of allergic mucin.

In some cases, patients may have more important symptomatology, like proptosis, telecanthus, craniofacial dysmorphia[41,42].

The main problem of the diagnostic is to differentiate AFRS from other fungal infections that affect paranasal sinuses, which include saprophytic fungal proliferation, mycetomas, eosinophilic rhinosinusitis and different forms of invasive fungal rhinosinusitis.

The most important part of the diagnosis of AFRS remains the histopathological examination. The usual stain is hematoxylin-eosin and it will help us identify the presence of inflammatory cells: eosinophils, plasma cells and lymphocytes[42]. The aspect of the sinus mucosa is hypertrophic and hyperplastic, but we do not observe any sign of tissue necrosis, invasion of the adjacent tissues or giant cells. We must remember that the characteristic aspect of the eosinophilic mucin is the most reliable indicator of this affection.

Other paraclinical investigations useful for the diagnosis of AFRS are imaging techniques. On CT scan, we will notice the unilaterality of the disease[42]; the AFRS aspects of computer tomography are very characteristic, being one of the elements for a positive diagnosis. They are represented by hypodense areas (areas of eosinophilic mucin protein), alternating with radiopaque areas, represented by the accumulation of calcium salts and metal from the eosinophilic mucin[43,44]. Bone erosions (Figure 3) are very common (between 20-98%, according to the authors), and most commonly occur in the ethmoid cells. The orbit is the most common site of the extension, due to the fragility of the lamina papyracea. Quite frequently intracranial extension is encountered, especially in the anterior cerebral fossa, but sometimes the middle or posterior cerebral fossae may be involved[45,46].

MRI reveals hypointense central areas or lack of signal on T1/T2, with increased signal on peripheral T1 and T2[47]. Magnetic resonance imaging has been demonstrated to have an increased specificity for AFRS, especially when it is combined with CT imaging[48]. It is important to examine with attention the CT or MRI scans before the surgery, because it helps us to differentiate between AFRS and invasive fungal sinusitis or rhinosinusal malignancies, in order to prevent any exaggerated open or radical surgical procedures in these cases.

3. Invasive fungal rhinosinusitis (IFS)

Invasive fungal rhinosinusitis (IFS) is a condition that requires urgent diagnosis and early treatment, be-

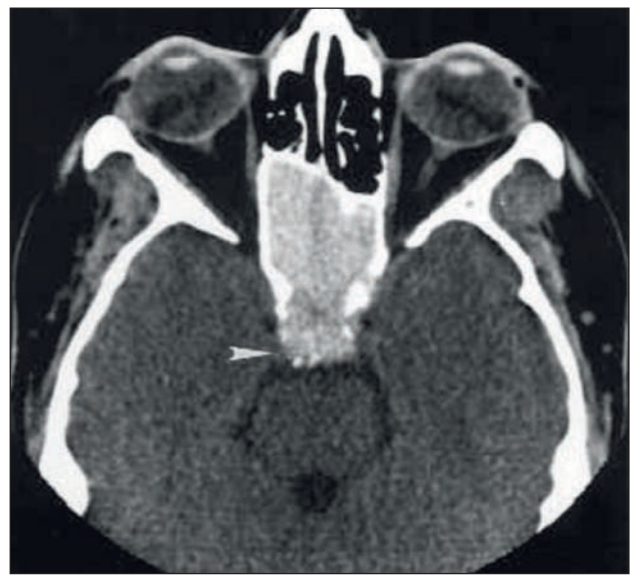

Figure 3 CT scan – axial section; bilateral spheno-etmoidal opacity, with clivus erosion and extension to the posterior cerebral fossa (arrow)

cause of its reserved vital and functional prognosis. Essentially, this condition occurs in immunocompromised patients, such as those with immunosuppressive therapy, bone marrow transplants, organ transplants, HIV-infected patients, the corticodependents, diabetics with protein malnutrition, etc. Much less often (but cases were nevertheless reported), IFS can appear in immunocompetent patients. Thus, the majority of patients with IFS have already a poor physical condition, because of the previous diseases or treatment related; in these circumstances, a reserved prognosis and a high mortality are expected. These factors contribute to increased difficulties in diagnosis and treatment of IFS that can quickly progress, with great damage. Therefore, the diagnosis must be established as early as possible, in order to initiate aggressive surgical and systemic antifungal therapies.

For the diagnosis of IFS, there are some proposed diagnostic criteria: (1) rhinosinusitis confirmed radiographically and (2) histopathological evidence of fungal invasion of the sinus mucosa, submucosa, blood vessels or bones[49].

Therefore, clinical suspicion of fungal rhinosinusitis is difficult to be formulated based only on symptomatology; fungal etiology should be considered also in those cases of chronic rhinosinusitis rebel to prolonged antibiotherapy[50-52].

The most common sign is represented by ischemic nasal mucosa, areas of pale, edematous mucosa. Although the emergence of a black eschar is considered almost pathognomonic for IFS, it is usually a late discovery due to vascular thrombosis and tissue necrosis.

ENT clinical examination can provide important diagnostic information in patients with risk factors for fungal rhinosinusitis. The most common sign we encounter when examining the nose is an ischemic or edematous mucosa, which bleeds very little and is painful when performing various invasive maneuvers. Black eschars usually appear in the late phases of the disease, due to thrombosis and tissue necrosis. In cases when the orbit is involved, we may find limitations of the extraocular movements, proptosis or reduced vision. The invasiveness potential of the disease may determine affection of the skin, hard and soft palate or intracranial extension, which should exclude the diagnosis of bacterial infection[52].

Great help is provided by imaging techniques, especial computer tomography. Although many CT aspects for IFS have been reported as suggestive, none of them have been established as being pathognomonic[53]. Some studies[53] reported that fatty tissue infiltration can be made periantrally, and it "may represent the earliest imaging evidence of invasive fungal disease". Other authors[54] observe that sinusal mucosa thickening with unilateral nasal inflammation found in patients at risk may represent early predictive signs of IFS (Figure 4).

Magnetic resonance imaging (MRI) should be performed in the case of patients with suspected intracranial extension of IFS, this test being more sensitive in identifying intracranial or orbital lesions[54].

Histopathological examination is essential and it is the one that can diagnose with certitude the disease[55], by revealing the presence of necrosis, inflammation and mycelial filaments.

CONCLUSIONS

Fungal sinusitis could be one of the most challenging affections that the otolaryngology doctor could diagnose and treat. Because of its invasiveness potential, especially in patients at risk, it is essential to have a correct and fast diagnosis in case of fungal rhinosinusitis, in order to begin the treatment as fast as possible, for a favourable prognosis. The only way to establish the diagnosis in a reliable way is to make a detailed clinical examination and to take biopsy samples.

In order to diagnose fungal rhinosinusitis, two essential conditions are necessary: diagnosis of rhinosinusitis (we must not forget the ubiquitous nature of fungi) and proving the existence of fungal infection. The latter can be achieved by pathological and/or mycological examinations. Histopathology remains the benchmark, based on the literature data, that gives the best sensitivity in detecting rhinosinusal fungal infections. Mycological examination is a useful and has a certain value, but it involves special conditions for harvesting, transporting and processing in order to obtain positive results.

Unfortunately, we do not have any standard criteria for the imaging diagnosis of fungal rhinosinusitis. The most useful imaging technique remains the CT scan, because of its ability to identify the signs in early stages, due to increased sensitivity, but low specificity for this disease. The CT scan should be made at 3-mm inter-

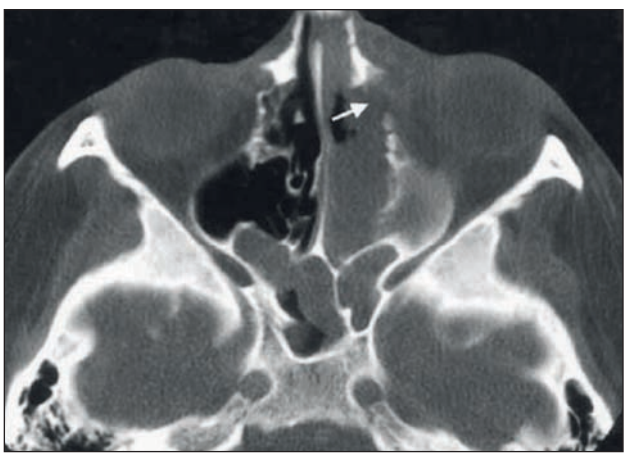

Figure 4 CT scan – axial section, bony erosion of the left lamina papiracea, with intraorbital invasion

vals in axial and coronal planes, using both bone and soft tissue windows. MRI exams have limited value and may serve as diagnostic methods, possibly representing a starting point for the diagnosis of these clinical entities, but they are most often required to double the computer tomography examination.

Despite all the studies that were conducted in the past years, this disease remains surrounded by controversies. New researches of the etiopathogeny, as well as advances in diagnosis and treatment, will determine an improved prognosis.

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