DIAGNOSIS AND MANAGEMENT OF FUNGAL RHINOSINUSITIS

DIAGNOSTIC ET PRISE EN CHARGE THÉRAPEUTIQUE DES RHINOSINUSITIS FONGIQUES

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ABSTRACT

Introduction: In recent years, interest in the fungal pathology of the rhinosinus has been renewed, and numerous studies have been published on the possible responsibility of fungal agents in rhinosinus pathologies.

Objective: To study clinico radiological characteristics of fungal rhinosinusitis and discuss therapeutic modalities of this entity.

Methods: This is a retrospective descriptive study conducted at the ENT and cervicofacial surgery department, which enrolled patients treated for rhinosinusitis over a 20-year period.

Results: Our study included 45 patients treated for fungal rhinosinusitis. Fungal ball (22 cases) was the most frequent entity. Dental origin was found in 15 patients. Facial imaging (CT+/-MRI) was performed in all cases. Mycological examination was positive in 19 patients. Forty-one patients (91%) underwent exclusive endonasal surgery under endoscopic guidance. Pathological examination was suggestive of sinonasal aspergillosis in 20 cases. Nine patients were treated with antifungal agents. Local recurrence was noted in four patients after an average follow-up of 14 months.

Conclusions: Fungal rhinosinusitis is the leading cause of chronic unilateral sinusitis in adults. Despite improvements in diagnostic methods, uncertainties persist concerning pathophysiological mechanisms, diagnostic criteria and therapeutic attitudes.

Keywords: Fungal sinusitis - Imaging - Endoscopic surgery - Anti-fungal treatment

RÉSUMÉ

Introduction: La pathologie fongique rhinosinusienne a connu ces dernières années un regain d'intérêt et de nombreux travaux ont été publiés sur l'éventuelle responsabilité des agents fongiques dans les pathologies rhinosinusiennes.

Objectifs: Etudier les caractéristiques clinico radiologiques des rhinosinusites fongiques et discuter leurs modalités thérapeutiques.

Méthodes: Il s'agit d'une étude rétrospective descriptive menée au service ORL et CCF ayant colligé les malades pris en charge pour une rhinosinusite fongique, sur une période de 20 ans.

Résultats: La moyenne d'âge des patients était de 54,2 ans. Une prédominance féminine a été notée avec un sex ratio H/F à 0,87. La balle fongique ou mycétome était la forme la plus fréquente (22 cas). L'origine dentaire a été retrouvée chez 15 patients dans notre série. Le délai moyen de consultation était de 16 mois. Une imagerie du massif facial (TDM+/-IRM) a été réalisée dans tous les cas. L'examen mycologique était positif chez 19 patients. Quarante-un patients (91%) étaient opérés par voie endonasale exclusive sous guidage endoscopique. L'examen anatomopathologique était évocateur d'aspergillose nasosinusienne dans 20 cas. Neuf patients étaient mis sous traitement antifongique. Une récidive locale a été notée chez quatre patients après un suivi moyen de 14 mois.

Conclusion: Les rhinosinusites fongiques sont la première cause de sinusite unilatérale chronique de l'adulte. Malgré l'amélioration des moyens diagnostiques, des incertitudes persistent concernant les mécanismes physiopathologiques, les critères diagnostiques et l'attitude thérapeutique.

Mots clés: Sinusite fongique – Mycose – Chirurgie endonasale – Traitement anti fongique

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INTRODUCTION

Fungal sinusitis is a condition that has been well documented for many years. In recent years, attention has returned to rhinosinus conditions of fungal origin, and numerous studies have been published examining the role of fungal agents in these disorders. Inhaling these microorganisms can lead to the development of both acute and chronic rhinosinusitis. The interaction between fungal agents and sinonasal cavities results in a wide range of conditions. Clinical features vary according to the fungal agent, the patient's immune status and the local condition of the mucosa [1, 2]. The increase in their incidence in recent years is explained by improved means of exploration and the appearance of new risk factors such as the widespread use of antibiotics and corticosteroids [1, 3].

Diagnosis is often delayed and difficult, given the varied and non-specific nature of the clinical signs. Invasive forms represent a diagnostic and therapeutic emergency, threatening the patient's vital and functional prognosis. Therapeutic management remains controversial. It depends on the form and type of causatif agent [4].

Our aim was to present the clinic radiological features of fungal rhinosinusitis and discuss therapeutic modalities of this entity.

MATERIALS AND METHODS

This is a retrospective study of patients treated for fungal sinusitis at our department, over a 20-year period (January 2000 - December 2019).

Were included in this study all patients treated for fungal sinusitis and whose diagnosis was confirmed through anatomopathological and/or mycological examinations. In instances where histological examination or mycological sampling did not provide conclusive evidence, the diagnosis of fungal rhinosinusitis was established based on diagnostic criteria. This included assessing radiological features through CT or MRI scans, evaluating macroscopic findings during nasal endoscopy, and identifying typical or suggestive characteristics of fungal sinusitis during surgical procedures.

We excluded from our study patients with unusable records due to lack of imaging data and results of complementary examinations (3 cases) and patients lost to follow-up immediately after surgery (4 cases).

Data collected from patients included age, gender, associated comorbidities and clinical symptoms and signs, including complications that patients presented at the time of consultation. Variables also included imaging, microbiological and pathological findings, as well as therapeutic modalities. Data were entered and analyzed using SPSS version 22 software.

RESULTS

In our study, 45 cases of fungal rhinosinusitis were recorded. The average age of patients was 54.2 years (19 - 85 years), with a sex ratio of 0.87. Patients diagnosed with fungal rhinosinusitis were classified into four categories: Mycetoma or aspergilloma: 22 cases (48.9%), Allergic fungal rhinosinusitis (AFRS): 10 cases (22.2%), Chronic invasive form: 8 cases (17.7%) Acute invasive form (Mucormycosis): 5 cases (11.1%) on the basis of histopathological and mycological examinations.

A history of dental extraction and root canal treatment was noted in 15 cases. Chronic rhinosinusitis with polyps resistant to medical treatment was found in 5 patients in our series. A history of sinonasal surgery was found in 3 cases. All patients with mucormycosis were immunocompromised (diabetes mellitus with ketoacid decompensation in all 5 patients, systemic lupus erythematosus had received corticosteroid therapy in one patient, chronic renal failure hemodialysis stage in one patient).

The average consultation time in our series was 16 months, with extremes ranging from 7 days to 48 months. The clinical symptoms were not very specific. They were dominated by nasal obstruction in 82% of cases, rhinorrhea in 60% and headache in 40%.

On clinical examination, stigmata of amalgam dental care were found in 7 patients, dental caries in 5 patients, necrosis of the hard palate in two patients diagnosed with mucormycosis, and exophthalmos in 8 cases. Palpebral edema was present in 5 cases. A patient diagnosed with mucormycosis presented with a permeation nodule of the lower eyelid. Cranial nerve involvement was observed in five mucormycosis patients on neurological examination (peripheral facial paralysis in two patients and oculomotor paralysis in 04 patients).

Diagnostic nasal endoscopy revealed nasal polyps in 62.2% of cases (28 patients), purulent nasal discharge in 42.2% of cases (19 patients) and the presence of necrotic lesions in 6.6% of patients (3 patients).

All patients underwent facial CT scans. Sinus involvement was unilateral in 36 patients and bilateral in 9 patients. The most frequently affected sinus was the maxillary sinus. Imaging suggested fungal sinusitis in 60% of cases: It evoked the diagnostic of fungal ball in 78% in front of the presence of a metallic-toned foreign body or microcalcifications within a total or partial filling of the concerned sinus (Fig.1).

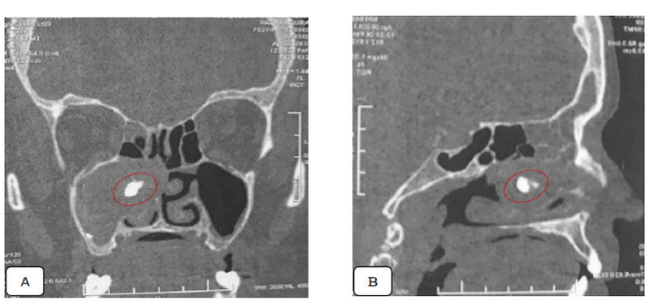

Figure 1: CT scan of the facial mass in axial (A) and sagittal (B) sections showing total filling of the right maxillary sinus, including a dense foreign body (red circle) (Fungal bullet)

For AFRS, the presence of heterogeneous filling containing hyperdense zones was noted in 4cases. Bone lysis was present in 85% of cases of mucormycosis and 62% of pseudotumor rhinosinusitis, versus 13-20% in non-invasive localized forms. Endocranial extension was observed in 3 cases and orbital extension in 7 cases (Table 1).

Table 1: CT scan of patients according to clinical form

Scanographic appearance		Mycetoma (Fungal Ball)	AFRS	CIFR	AIFR
Intrasinus foreign body		1case	-	-	-
Orbital extension		-	1 case	3 cases	4 cases
Calcifications		8 cases	4 cases	2 cases	-
Homogeneous filling		8 cases	4 cases	3 cases	2 cases
Heterogeneous filling		14 cases	6 cases	5 cases	3 cases
Septal deviation		8 cases	2 cases	2 cases	-
Endocranial extension		-	-	-	3 cases
Extension to the nasal cavity		13 cases	9 cases	3 cases	3 cases
Lysis Bone	Inter sinus-nasal septum	3 cases	2 cases	2 cases	4 cases
	lamina papyracea	1 case	-	2 cases	1 case
	Internal wall of MS	-	1 case	2 cases	2 cases
	Orbit floor	-	1 case	1 case	3 cases
	Ethmoid roof	1 case	1 case	-	-
Cavernous sinus thrombosis		-	-	-	2 cases
Concha bullosa		2 cases	3 cases	1 case	-

AIFR: Acute invasive fungal rhinosinusitis; CIFR: Chroni invasive fungal rhinosinusitis; AFRS: Allergic fungal rhinosinusitis

MRI was performed in 10 patients, in view of the presence of orbital and/or endocranial extension: four cases of allergic fungal rhinosinusitis (Fig.2), three cases of fungus mycetoma, two cases of chronic pseudotumor sinusitis and one case of mucormycosis.

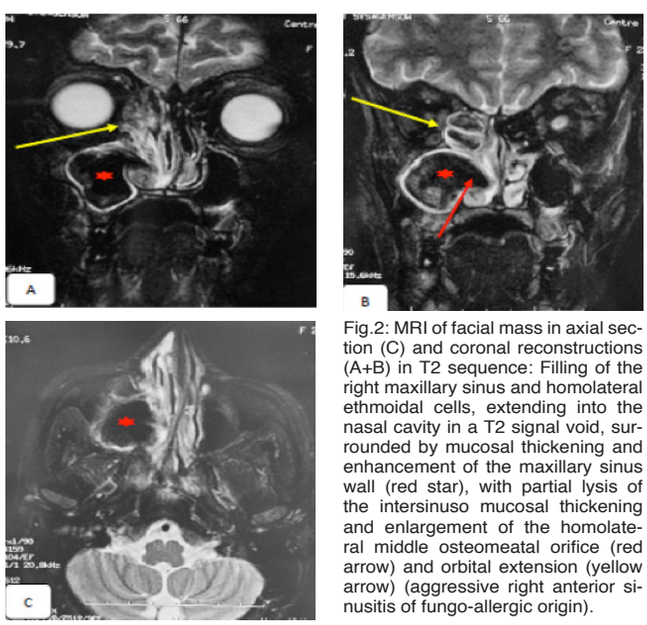

Fig.2: MRI of facial mass in axial section (C) and coronal reconstructions (A+B) in T2 sequence: Filling of the right maxillary sinus and homolateral ethmoidal cells, extending into the nasal cavity in a T2 signal void, surrounded by mucosal thickening and enhancement of the maxillary sinus wall (red star), with partial lysis of the intersinuso mucosal thickening and enlargement of the homolateral middle osteomeatal orifice (red arrow) and orbital extension (yellow arrow) (aggressive right anterior sinusitis of fungo-allergic origin).

The immunoallergic tests were performed in cases of AFS. They showed hypereosinophilia in all cases, and elevated Aspergillus-specific IgE in three cases. Skin prick testing was not realized. Aspergillosis serology was performed in four cases, and was positive in only one patient. Mycological examination was performed on 26 patients (or 57.7%) and was positive in 19 cases with sensitivity of 73%, showing the presence of mycelial filaments, of which three cases were suggestive of mucoral genus. Culture was positive in 13 cases. It revealed aspergillus fumigatus in seven cases, aspergillus flavus in two cases, candida glabrata in one case and mucor in three cases.

Anatomopathological examination, performed on all our patients, confirmed the diagnosis in 22 cases (or 49%), showing aspergillary filaments in 19 and mucoral filaments in 3 cases. Hypereosinophilia was observed in 14 cases. The mucosa was inflammatory with the presence of non-specific granulation tissue in 4 patients. The diagnosis of mucormycosis was confirmed in all cases by anatomopathological examination.

All our patients underwent surgery. The aim is to completely remove the fungal lesions and restore permeability to the ostio-meatal complex. For the locally non-invasive form, treatment was exclusively surgical. The endonasal approach was exclusive in 41 patients. The other four patients underwent combined surgery, with a Caldwell-Luc approach in two cases, a para lateronasal approach in one case and a Cairn Unterberger bicoronal approach in one case.

For patients diagnosed with fungus ball, surgery was performed by the endoscopic approach in 21 patients, depending on the topography of the lesion. The Caldwell-Luc approach was indicated in one patient with several intraoperative aspergillary truffles in the maxillary sinus, which were difficult to extract using the endoscopic approach alone.

For patients with AFRS, endonasal surgical treatment was combined with local postoperative corticosteroid therapy in all cases, and oral corticosteroids in 4 cases. Antifungal treatment with voriconazole was indicated in 3 patients.

Surgery was performed by endonasal approach for 7 patients presenting chronic invasive form. A coronal external approach was considered necessary in one case. Antifungal treatment with voriconazole was indicated in one patient for orbital extension.

In the cases of mucormycosis, treatment was as early as diagnosis was confirmed. A paralateronasal rhinotomy was performed in one case. A Caldwell-Luc approach in association with the endonasal endoscopic approach was performed in one case, and the exclusive endonasal endoscopic approach in three cases. Surgical debridement of necrotic tissue combined with parenteral Amphotericin B was performed in all cases at a dose of 1.5mg/ kg/day for 8 to 49 days. Insulin therapy, correction of metabolic disorders and treatment of renal insufficiency were provided to all patients.

Follow-up was clinical and radiological. The average time interval for follow-up in our study was 14 months.
Progression was favorable in most patients. In the fungal ball form, recurrence was noted at 16 months and 5 months in two patients operated on via the endonasal and external Caldwell-Luc approaches respectively. Both patients underwent endonasal reoperation (middle meatotomy) with good outcome. One patient diagnosed with AFRS presented a bilateral recurrence of rhinosinusitis 2 years postoperatively. She underwent endonasal reoperation and antifungal treatment. One patient treated for mucormycosis presented with recurrence at postoperative day 60, treated with Amphotericin B with a favorable outcome. The three other patients diagnosed with mucormycosis died following rhythm and ionic disorders in multi-tared patients in decompensation (Table 2).

Table 2: Summary table of clinical presentation and therapeutic approaches of the different forms of fungal infections in our series

	Clinical presentation	Histology	Mycology	Medical treatment	Surgical treatment	Evolution
Mycetoma (Fungal Ball) (22 cases)	-History of dental care in 13 cases -Diabetes: 7 cases → Nasal obstruction , headache	Aspergillosis: 15 cases	-Mycelial filaments: 7 cases -Positive Culture: 3 cases (2 Asp Fumigates; 1 Asp Flavus	post operative antibiotics	-middle meatotomy (MM): 19 cases -sphenoidotomy :2 cases -MM +Caldwell-Luc: 1 case	Favorable: 20 cases 2 recurrences ⊠MM
AFRS (10 cases)	History of asthma: 4 cases, diabetes:1 case →Nasal obstruction, headache, rhinorrhea, smell disorders exophthalmos and infraorbital edema: 2 cases	Inflammatory polyps: 10 cases	-Mycelial filaments: 4 cases -Positive culture : 3 cases (2Asp Fumigatus, 1Asp Flavus	Oral corticosteroids: 4 cases Voriconazole: 3 cases	endonasal endoscopic approach (MM+ethmoidectmy+/-sphenoidotomy): 10 cases	Favorable: 9 cases recurrence: 1 case treated with endoscopic approach
CIFR (8 cases)	History of dental care in 2 cases; diabetes:1 case → Nasal obstruction, headache, smell disorders exophthalmos: 1 case; eyelid edema: 2 cases	-Aspergillosis: 2 cases -Inflammatory mucosa: 6 cases	-Mycelial filaments: 3 cases -Positive culture : 2 cases (1Asp Fumigatus; 1Candida Glabrata)	Voriconazole:1 case	-Endonasal approach (MM+ ethmoidectmy+/-sphenoidotomy) for 7 patients -coronal external approach +EA: 1 case	Favorable: 8 cases
AIFR (5 cases)	diabetes : 5 cas systemic lupus :1 case chronic renal failure : 1 case → ocular orbital symptoms, Cranial nerve involvement	mucormycosis: 5 cases	-2 Asp Fumigatus -mycelial filaments of the genus mucorale: 3 cases	Amphotericin B : 5 cases	Surgical debridement: *paralatero nasal rhinotomy: 1 case *Caldwell-Luc + endoscopic approach: 1 case *Endoscopic approach: 3 cases	-3 cases of death -recurrence: 1 case

AIFR: Acute invasive fungal rhinosinusitis; **CIFR:** Chroni invasive fungal rhinosinusitis; **AFRS:** Allergic fungal rhinosinusitis; **Asp: Aspergillus; MM:** middle meatotomy

DISCUSSION

Sinus involvement by fungal agents was first described in 1791 by Plaignaud as a fungal tumor of the maxillary sinus, then by Zarniko in 1891 [5].
The incidence of fungal sinusitis has risen over the last few decades, from 13% to 45%. The excessive use of antibiotics, antihistamines and corticosteroids in the treatment of allergic rhinitis and sinusitis can play a role in the destruction of bacterial flora. This disease is more common in rural areas, where exposure to dust is more frequent, and in regions with a dry and hot climate [2,6]. Several other factors favor the onset of fungal rhinosinusitis, such as hypoxia, temperature variations, dehydration, foreign bodies, infection, trauma, tobacco, environmental pollutants and allergens. Dental etiology is the most common cause of aspergillary grafting in fungal ball [7,8]. Immunocompromised people, such as patients with HIV, diabetes mellitus, taking long-term corticosteroids or certain autoimmune diseases, are more likely to develop invasive fungal sinusitis due to their weakened immune system [3].
Fungal rhinosinusitis, either invasive or non-invasive, present different clinical signs. In the non-invasive form, patients may experience persistent nasal congestion, unilateral or bilateral rhinorrhea, anosmia and headache [6]. Symptoms of the invasive form are more severe and include rhinosinus, orbital and occasionally neurological signs [3,9]. Early recognition of these signs is essential for accurate diagnosis and appropriate intervention [10, 11].
To establish an accurate diagnosis of fungal rhinosinusitis, whether invasive or non-invasive, several additional exams are essential to confirm the presence of the infection and assess its extent.
Radiological exploration has an essential place. Sinus computed tomography (CT) should be performed as the initial diagnostic step in cases of chronic sinusitis unresponsive to medical treatment. It visualizes the typical changes associated with this pathology, such as the presence of fungal masses in the sinus cavities. Specific radiological criteria are used to assess the likelihood of the disease [12]. In the case of invasive fungal rhinosinusitis, accurate and rapid diagnosis is essential due to its aggressive nature.
CT scan of the facial mass is particularly useful for guiding the surgical procedure. Radiological signs are highly variable, depending on the type of fungal infection [12,13].
Magnetic resonance imaging (MRI), can be used to assess the progression of infection in surrounding tissues and to determine the extent of fungal invasion.
In our series, facial MRI was requested in 10 patients

(three cases of fungal bullet, four cases of AFRS, two cases of CIFR and one case of mucormycosis).

A mycological examination should be requested systematically. A positive examination establishes with certainty the diagnosis of mycosis. Using specialized cultures, it identifies the species involved and tests its sensitivity to various antifungal agents [14]. To make a definitive diagnosis of fungal sinusitis, direct examination must reveal the fungal agent in its mycelial form. Its sensitivity varies from 72% to 94% [15,16]. In our series, direct examination was carried out on 26 patients and was positive in 19 cases, with a sensitivity of 73%.

In cases of mucormycosis, it allows a rapid diagnosis by distinguishing septate filaments of the aspergillus genus from non-septate filaments of the mucoral genus [17]. In the literature, culture is positive in only 30% to 50% of cases [15,16]. It is particularly difficult and rarely positive in mucormycosis [17,18]. In our series, the culture was positive in 13 cases, or 50% of the total. Zuluaga et al found in their series a dominance of aspergillus fumigatus, while the study by Sasso et al found a dominance of aspergillus spp [15].

In our series, Aspergillus fumigatus was the most frequently encountered species. It was encountered in 4 cases of non-invasive fungal sinusitis (two cases of fungal bullet and one case of AFRS) and in two cases of mucormycosis.

Anatomopathological examination confirms the diagnosis of fungal rhinosinusitis. Endoscopic biopsy is used to obtain tissue samples for microscopic analysis, identifying mycelial filaments whose morphology can be used to classify the disease. It also distinguishes between invasive and non-invasive forms.

In both types of fungal rhinosinusitis, the patient's immune status can be evaluated. Immunoallergic and serological tests are carried out to determine whether there are any underlying immune factors that might predispose the patient to this condition.

Immunoallergic tests (Eosinophilia, total serum IgE, specific serum IgE and skin tests) are necessary for nosologic individualization of AFRS, but is not always positive [19]. In our series, aspergillus-specific IgE was elevated in three patients diagnosed with AFR, with levels of 224, 250 and 274 units. Hypereosinophilia was found in 13 patients in our series (10 cases of AFRS, two cases of CIRS and one case of mucormycosis).

A positive aspergillosis serology indicates invasive aspergillosis rhinosinusitis. It is positive in only 64% of cases [20]. In our series, aspergillosis serology was performed in 4 patients, and came back positive in only one patient diagnosed with AFRS.

Antigen tests, such as galactomannan and βD-glucane tests, are only helpful against some pathogens [17,21]. This test is available in Tunisia, but was not carried out in our series.

Molecular tests such as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) are very promising, but are very costly and have yet to be clinically validated [2, 22, 23].

Management of fungal rhinosinusitis requires a multidisciplinary approach. Management is often medico-surgical.

Endonasal surgery is the technique of choice for the treatment of sinusitis in order to preserve the mucosa as much as possible, to allow proper nasal and sinus ventilation and regeneration of mucociliary clearance. Surgical procedures performed are adapted to the sinus involvement (middle meatotomy, ethmoidectomy, sphenoidotomy...).

The external approach is most often recommended in case of failure or inaccessibility of lesions by endoscopic approach or in cases of extra-sinus invasion, particularly intraorbital or endocranial [24]. In our series, two patients underwent Caldwell-Luc vestibular surgery. A patient with rhino-orbito-cerebral mucormycosis underwent paralateronasal approach surgery.

The use of antifungal agents is controversial depending on the type of fungal infection.

Medical management for AFRS is still controversial. The most recommended approach is to combine surgical treatment with long-term oral and/or local corticosteroid therapy [1,3,19]. Most authors consider that systemic antifungal agents have not been shown to be effective and are not justified for extra-mucosal pathology. On the other hand, other authors have noted a clinical improvement after the use of oral Itraconazole [25]. In our series, two patients underwent fungal treatment for intraorbital extension. Immunotherapy can be proposed as a complement to wide surgical debridement and corticosteroid therapy [26, 27].

For invasive fungal rhionsinusitis, a medico-surgical treatment should be combined with the management of underlying defects. Amphotericin B remains the antifungal of choice for mucormycosis, at an optimal dose of 1 to 1.5 mg/kg [4,28].Voriconazole is becoming an option for patients with Aspergillus. It has a better side-effect profile, but is less effective against Mucorales [29]. Other antifungal drugs (Posaconazole, Isavuconazole) are also available but, reserved for second-line treatment and require larger databases [29]. Close collaboration with microbiologists is essential for proper management. Some publications contain limited data on the use of hyperbaric oxygen therapy as a complementary treatment approach. Although the available data are limited, they suggest greater potential benefits for diabetic patients [30]. Treatment of underlying pathologies is an important step in ensuring the efficacy of treatment and the proper evolution of the disease, such as balancing diabetic acidosis, remission of leukemia, and reducing the dose of immunosuppressants in the event of organ transplantation, if possible [10].

The results of non-invasive treatment of fungal rhinosinusitis vary according to the type of rhinosinusitis. In the case of fungal ball, recurrence is rare, with reported rates ranging from 0.03% to 0.2% [31, 32].

Recurrences are frequent in cases of AFRS (10 to 75%) [3,6]. These recurrences may occur several years later, despite initial treatment.

In the case of CIFR the prognosis depends on the rapidity of treatment and the underlying terrain. If the diagnosis is made at an early stage, before orbital and endocranial extension, evolution is good in the majority of cases. However, in advanced forms, the prognosis becomes more serious and may be life-threatening. In 28% of immunocompetent subjects, the disease is fatal. The prognosis of acute invasive fungal sinusitis is often very poor, with mortality of 20-80% [3,4].

At the end of this work and after review of the literature, we propose two algorithms for the diagnostic approach and therapeutic management for fungal rhinosinusitis (Fig. 3 and 4).

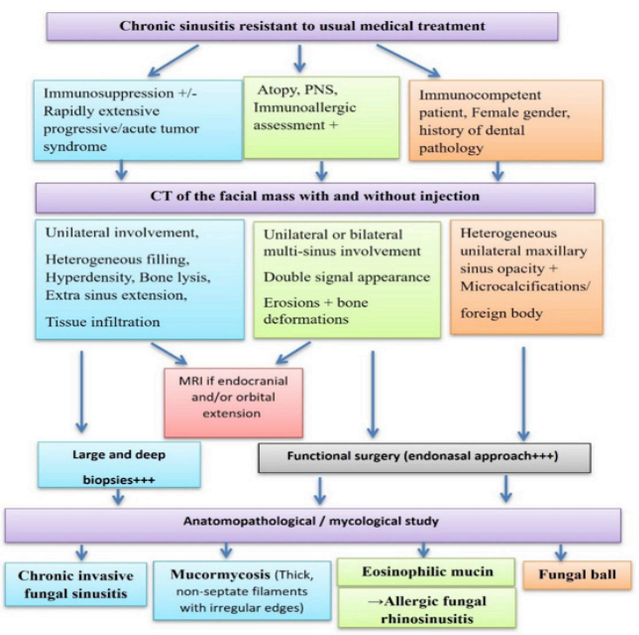

Figure 3: Diagnostic approach algorithm for suspected fungal rhinosinusitis

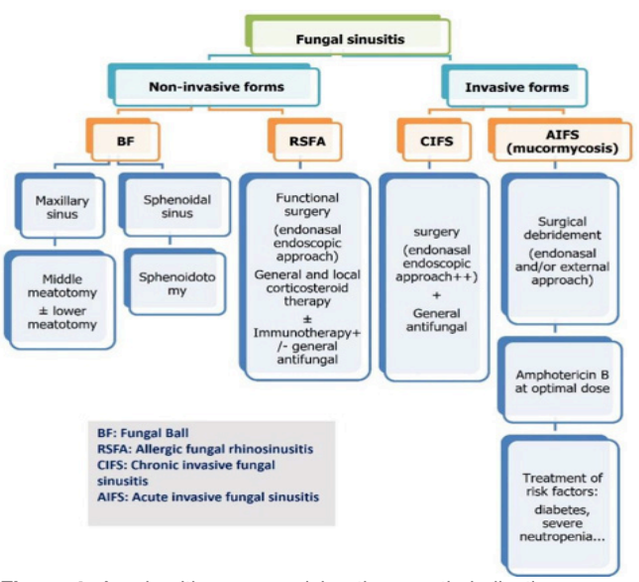

Figure 4: An algorithm summarizing therapeutic indications according to the type of fungal sinusitis and its location

CONCLUSION

Fungal rhinosinusitis is a complex pathology that has attracted growing interest over the years. This condition, caused by fungal infection of the sinuses and respiratory tract, requires a rigorous diagnostic and therapeutic approach. Treatment of this disease often involves the use of antifungals, corticosteroids and surgery. However, regular follow-up of patients is essential to ensure effective management and prevent recurrences. Ultimately, an approach is essential to improve the management of patients with fungal rhinosinusitis and to continue advancing knowledge of this complex medical condition.

Ethical considerations: The ethics committee accord of our hospital was not necessary when conducting our work, due to the retrospective nature of the study, without experimental intervention with respect for the anonymity of the patients.

Conflict of interest: All authors declared none conflict of interests.

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