Journal of Cranio-Maxillo-Facial Surgery 44 (2016) 512–520

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

# Invasive fungal rhinosinusitis in adult patients: Our experience in diagnosis and management

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ARTICLE INFO

*Article history:*
Paper received 6 August 2015
Accepted 30 December 2015
Available online 9 January 2016

*Keywords:*
Fungal rhinosinusitis
Mycosis
Skull base
Endoscopic sinus surgery
Aspergillus
Mucor

ABSTRACT

*Background:* This paper describes our experience in the management of acute and chronic invasive fungal rhinosinusitis (IFRS) in adults.
*Methods:* Medical files of all patients aged >18 years treated in our institutions for IFRS from 2002 to 2013 were retrospectively reviewed.
*Results:* A total of 18 cases (10 acute and 8 chronic) were recorded. In acute form, haematological malignancies represented the principal comorbidity (100%), while in chronic form this was diabetes mellitus (87.5%). All patients received systemic antifungal agents. Endoscopic sinus surgery was performed in 16/18 patients (88.9%). Among patients with an acute IFRS, 4/10 died of fungal infection (40%), on the other side 2/8 patients with chronic IFRS died of the evolution of the mycosis (25%).
*Conclusions:* Acute and chronic IFRS are different entities: in acute form, prognosis is poor, so therapy should be promptly performed, although host immune status and evolution of the haematological disease are key factors for the outcome. In chronic form, a wide surgical excision of the disease is recommended in order to obtain a complete removal of fungal infection. In both forms, early clinical findings are non-specific and ambiguous, so diagnosis depends on a high index of suspicion, taking into account predisposing factors.


## 1. Introduction

Fungal rhinosinusitis (FRS) can be divided into two categories based on histopathological findings: invasive and noninvasive, depending on fungal invasion of the mucosal layer. The first published attempt to classify FRS came in 1965, when Hora recognized two categories: noninvasive, behaving clinically like chronic bacterial sinusitis, and invasive, in which the infection results in a mass that behaves like a malignant neoplasm, eroding the bone and spreading into adjacent tissue (Hora, 1965). The invasive nature of the disease was further confirmed by histopathology (Jahrsdoerfer et al., 1979; Lowe and Bradley, 1986). In the late 1990s, deShazo proposed a new classification for invasive fungal rhinosinusitis (IFRS) based on clinical condition, immune status, histopathology, and fungal infection: acute (fulminant) invasive, granulomatous invasive and chronic invasive types (deShazo et al., 1997). Nowadays, the most commonly accepted classification divides FRS into invasive and noninvasive diseases based on histopathological evidence of tissue invasion by fungi. The noninvasive diseases include saprophytic fungal infestation, fungal ball and fungus-related eosinophilic FRS. IFRS include acute invasive (fulminant) fungal sinusitis, chronic invasive fungal sinusitis, and granulomatous invasive fungal sinusitis (Chakrabarti et al., 2009). Acute disease is when the duration of illness is <4 weeks, and chronic disease is

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http://dx.doi.org/10.1016/j.jcms.2015.12.016
1010-5182/

when the duration is >12 weeks, although other factors, such as host immune status, may also distinguish these two forms.

In the present study, we report the experience of two tertiary medical centres in the management of IFRS in adults. Preoperative diagnostic work up, surgical strategies, medical therapy, follow-up and outcome will be considered and discussed in this paper.

## 2. Methods

The study was conducted in two tertiary university-affiliated medical centres in Italy, the I.R.C.C.S. Policlinico San Matteo – University of Pavia and the Ospedale di Circolo e Fondazione Macchi – University of Insubria, Varese. All adult patients with IFRS observed and treated in our departments between January 2002 to December 2013 were included in the study; patients aged <18 years were excluded from this report. As stated by Local Ethics Committee ("Comitato Etico Locale"), patients gave their informed consent for data review for scientific purposes. We retrospectively reviewed medical files and data. Patients were divided according to the classification proposed by Chakrabarti et al. (Chakrabarti et al., 2009), based on time course of the disease (acute <4 weeks, chronic >12 weeks). All patients underwent nasal endoscopy, computer tomography (CT) and in some cases magnetic resonance imaging (MRI). Endoscopic mucosal biopsy and cultural samples were obtained during surgery on both the mucosal specimens and intrasinusal material. For microscopic examination, the specimen was homogenized in NaCl 0.9% sterile solution and was stained by Periodic Acid–Schiff, chromotroph-aniline blue, Gomori-Grocott methenamine silver nitrate and hematoxylin and eosin. *Aspergillus* and *Mucor* species were differentiated based on their histologic appearance. Cultural examination was performed in Sabouraud Dextrose Agar plus Chloramphenicol for isolation of the fungi. All patients received the best available standard of care for antifungal therapy: the choice of antifungal agents was managed by infectious disease specialists, according to published guidelines (Fisher et al., 1991; Herbrecht et al., 2002; Walsh et al., 2008; Cornely et al., 2014). Postoperative follow-up includes nasal endoscopy and an imaging study of the sinonasal, skull base and brain regions.

## 3. Results

### 3.1. Acute IFRS (Table 1)

A total of 18 cases of IFRS were observed; among these, 10 presented an acute form (55.6%). All patients with a diagnosis of acute IFRS were affected by hematological malignancies: in 5 patients (50%), an acute myeloid leukemia (AML), in 3 patients (30%) a myelodysplastic syndrome (MDS) and in 2 patients (20%) an acute B-cell lymphoblastic leukemia (B-ALL) was reported. In all of these cases, the infection developed during a severe neutropenic state (neutrophil count <500/mmc); the neutropenia was subsequent to chemotherapy in 8 patients (80%), while it was an expression of the patient's haematological disease in 2 cases (20%). The main symptom at onset was fever in 8 of 10 cases (80%); moreover, facial pain with or without facial swelling was present in 7 of 10 patients (70%). A prompt fiberoptic endoscopic evaluation of the nasal cavities confirmed the clinical suspicion of IFRS by the typical finding of ischemic or necrotic sinus mucosa. CT scan was at this point quickly performed, and a unilateral paranasal sinus involvement with opacification and hyperplastic mucosa was revealed in all cases. Among these patients, 8 of 10 (80%) underwent endoscopic sinus surgery (ESS); no haemorrhagic complications occurred despite severe thrombocytopenia. The other 2/10 patients (20%) did not undergo surgery for the very poor general conditions linked to the underlying disease. Surgery in acute IFRS should be tailored and modulated in relation to the site and extent of the sinonasal area involved by the fungal disease, as found intraoperatively. The goals of the surgery were removing all of the necrotic tissue to prevent progression of the disease, facilitating sinonasal ventilation and nasal irrigation, obtaining material for histopathological and cultural examinations, permitting postoperative medications (usually performed in the operating room) and endoscopic follow-up. Histological examination confirmed the invasive fungal disease in all cases. Microbiological analysis was also performed: in 8 cases (80%) *Aspergillus* was isolated, *Mucor* in 1 (10%), and both *Mucor* and *Fusarium* in 1 (10%). The mean time between symptom onset and surgery was 34.5 h (range 12–72 h). All patients promptly started a systemic anti-mycotic treatment usually with liposomal-Amphotericin B (Lipo-AmB) and Voriconazole (in some selected cases Itraconazole or Posaconazole were also used), as recommended after *Aspergillus* had been identified. Among the 10 patients treated, 4/10 died of progressive fungal infection (40%), 7, 12, 18 and 44 days after the diagnosis, in a phase of persistent neutropenia, while the mycosis improved substantially after complete neutrophil recovery in the other 6/10 (60%) patients. The overall recovery rate from IFRS in 8 patients that underwent ESS was 62.5% (5/8 patients). A clinical example of an acute IFRS is reported in Fig. 1.

### 3.2. Chronic IFRS (Table 2)

Among 18 patients with IFRS in our series, 8 presented a chronic form (44.4%). Patients with a diagnosis of chronic IFRS had an underlying non-hematological disease conditioning the immune status: in 7/8 cases (87.5%) a poorly controlled diabetes mellitus (DM) was recognized and 1 patient (12.5%) had a long-term systemic steroid treatment. Six patients (75%) had more than a single cause of immunosuppression. An important finding in the patients with a chronic IFRS was that the neutrophil count was normal or even higher in all of them. The most frequent symptoms at the onset of disease were headache (8/8 patients, 100%), decreasing in visual acuity or blindness (7/8 patients, 87.5%) and facial swelling (7/8 patients, 87.5%). All patients developed a progression of the disease toward the orbits and two patients intracranially. In one case, we observed a brain infarction and the consequent death of the patient. The surgical procedure was performed under endoscopic endonasal guidance in all patients. Biopsies were taken to confirm fungal invasion of the tissue. The complete removal of all necrotic tissue is recommended to be performed; thus, complete antero–posterior ethmoidectomy and sphenoidotomy were carried out. All of the ethmoidal cells had to be opened and the involved tissue was removed. The margins of resection were assigned by frozen sections. Informed consent about the possibility of an intraoperative switching from an endoscopic to a combined approach (endoscopic and external) was obtained in case of orbital invasion. In cases of decreased visual acuity without a clear involvement of the orbit (two patients in our series), an orbital and optic nerve decompression was immediately performed. If progression of the symptoms occurred, an orbital exenteration with the complete removal of the orbital contents was carried out in order to prevent intracranial involvement (one patient in our series). Three patients required surgery revision; the time from ED access to the first ESS varied from less than 1 day–7 months. No intraoperative complications occurred. Among patients with chronic IFRS histopathological samples documented *Mucorales* hyphae in tissue in 5 patients (62.5%) and invasive aspergillosis in the other 3 (37.5%) patients, whereas the cultures were positive in only 3 (37.5%) cases. After the diagnosis, all patients received a systemic therapy with the administration of antifungal agents: AmB-Lipo (3–5 mg/kg/