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Invasive fungal rhinosinusitis in immunocompromised patients*

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SUMMARY

***Introduction**: Invasive fungal rhinosinusitis (IFR) is one of the most important causes of morbidity and mortality in immunocompromised patients, principally those with cellular immunodeficiency, with mortality ranging from 50 to 80%. Prophylaxis and early diagnosis increase the chances of successful treatment.*

***Study design**: Clinical prospective randomized study.*

***Aim**: To present cases of IFR and to compare them with data reported in the literature.*

***Material and methods**: Analysis of eleven cases of IFR confirmed by pathologist examination.*

***Results**: Aspergillus was found to be the most prevalent pathogen. Symptoms ranged from high fever in most cases to nasal discharge, ulceration of the nasal mucosa, headache and periorbital edema.*

***Conclusion**: The combination of amphotericin B and endoscopic surgery, associated or not with Caldwell-Luc surgery, showed good results. The use of liposomal amphotericin B also presented a satisfactory outcome.*

Key words: rhinosinusitis, fungal infection, immunodeficiency.

INTRODUCTION

Invasive fungal rhinosinusitis is one of the most important causes of morbidity and mortality in immunosuppressed patients, especially those with leukemia and lymphomas or patients undergoing chemotherapy for bone marrow transplantation. Fungal rhinosinusitis was described by Berlinger et al. (1985) as a clinical entity characterized by infiltration of the mucosa by mycotic organisms, affecting bone and extending to the orbit and intracranial structures. Several cases involving both children and adults have been reported in the literature (Weber et al., 1987; Iwen et al., 1997; Rombaux et al., 1997; Gillespie et al., 1998), with mortality rates ranging from 50 to 80% (Waitzman et al., 1994).

The most common agents are *Aspergillus*, Mucoraceae, *Candida* and *Fusarium*, while infections with *Mucor* are less frequent. It is known that *Aspergillus* does not invade skin or intact mucosa but requires a previous lesion such as those resulting from nosebleed management or from local viral or bacterial infection. Therefore, these patients should receive careful treatment of low aggressiveness and any indication of infection should be considered important for their prognosis.

Diseases causing humoral immunosuppression such as AIDS, diabetes mellitus type I and chronic renal failure, among others, are more related to viral and bacterial infections, whereas immunodeficiencies caused by cellular suppression are more associated with fungal infections. Among them, neutropenia is directly associated with the prognosis of the patient. Another factor interfering with the course of the disease is the status of aeration of the paranasal sinuses, with individuals with impaired drainage of these cavities having a poorer prognosis.

The pathogenesis of invasive fungal rhinosinusitis is related to a reduction in cellular immunity. Thus, the treatment to be instituted should take into account specific antimicrobial drugs and surgical intervention, as well as improvement in the cellular response through stimulation of granulocyte growth factors, when necessary (Berlinger, 1985).

Since invasive fungal rhinosinusitis is a disease of high morbidity and mortality (Waitzaman et al., 1994; Iwen et al., 1997), prevention and an early and correct diagnosis of the disease are the best measures to avoid complications.

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The aim of the present study was to present recent cases of invasive fungal rhinosinusitis treated in a tertiary hospital and to compare them with data reported in the literature, with the main emphasis on aspects of treatment, symptomatology and evolution of the disease. The need for aggressive medical and radical surgical treatment of immunocompromised patients with fungal disease is emphasized.

MATERIAL AND METHODS

We conducted a retrospective study of 11 cases of invasive fungal rhinosinusitis confirmed by anatomopathological examination affecting immunocompromised patients treated between 1998 and 2001. Evolution of the patients and aspects of clinical and surgical treatment, as well as tomographic and endoscopic findings, were analyzed.

RESULTS

Four of the 11 patients with invasive fungal disease were males and seven were females, ranging in age from 17 to 63 years.

The associated immunosuppressive causes were hematologic disease in seven patients (63.6%), two of them undergoing chemotherapy, diabetes in one patient (9%), renal failure in one patient (9%), and secondary immunodeficiency (Acquired Immunodeficiency Syndrome, AIDS) in two patients (18.2%) (Table 1). Five (45.4%) of the 11 patients were infected with *Aspergillus flavus* and one (9%) with *A. fumigatus*. Three patients (27.2%) had invasive fungal disease caused by Mucoraceae and two patients (18.2%) presented non-specific hyphae. Two of the patients with *A. flavus* infection had associated pulmonary aspergillosis.

The predominant symptoms were persistent fever, nasal obstruction, headache, and purulent rhinorrhea, while periorbital edema was less common.

The tomographic findings are summarized in Table 2 and show various degrees of nasosinusal involvement.

All patients were submitted to surgical debridement combined with systemic antimycotic therapy including amphotericin B, fluconazole or ketoconazole immediately after the diagnosis of

Table 1. Summary of the cases showing the immunosuppressive disease and the etiologic agent of the fungal infection.

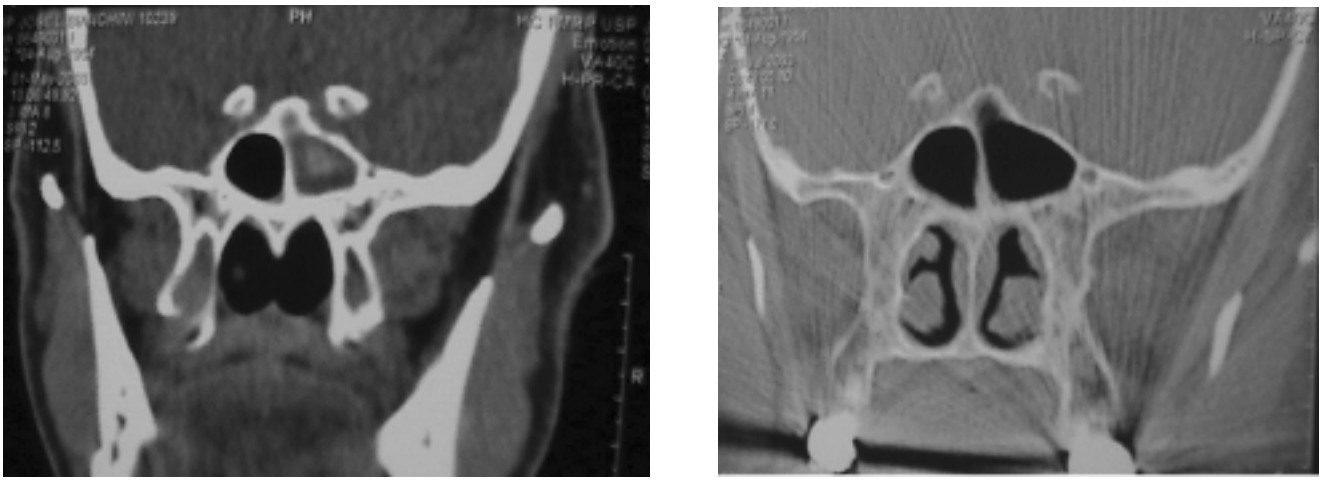
Patient	Base disease	Etiologic agent	Comments
1	Aplastic anemia	*Aspergillus flavus*	Hepatitis B
2	AML	Nonspecific hyphae	On chemotherapy
3	AIDS	*Aspergillus flavus*	----------
4	Diabetes mellitus I	Mucoraceae	----------
5	AML	*Aspergillus flavus*	Pulmonary aspergillosis
6	AML	*Aspergillus flavus*	On chemotherapy
7	AIDS	Nonspecific hyphae	----------
8	Chronic renal failure	*Aspergillus fumigatus*	----------
9	Aplastic anemia	Mucoraceae	Hepatitis B
10	AML	*Aspergillus flavus*	Pulmonary aspergillosis
11	Bone marrow aplasia	Mucoraceae	----------

AML = Acute Myeloid Leukemia

AIDS = Acquired Immunodeficiency Syndrome

Table 2. Fiberscopic and tomographic findings of fungal invasion.

Site of nasal lesion (fibroscopy)	Tomographic findings
1-Left inferior turbinate	Involvement of the nasal cavity, and ethmoid, maxillary, frontal and left sphenoid bone
2-Left inferior turbinate	Enlargement of the soft parts of the left lateral nasal wall and left maxillary mucosal thickening
3----------	Sphenoidal opacification
4----------	Ethmoidal opacification and right maxillary mucosal thickening with lysis of the lateral nasal wall
5-Crusts and purulent secretion in both middle meatus	Right frontal and bilateral maxillary opacification
6-Crusts and secretion on the right lateral wall	Enlargement of the soft parts of the left lateral nasal wall and right maxillary mucosal thickening
7-Anterior septal perforation, crusts and secretion on the right lateral wall	Maxillary mucosal thickening and infiltration with lysis of the septum, middle turbinate, maxillary middle wall and right ethmoidal floor
8-Polyp in the left middle meatus	Left frontomaxillary ethmoidal opacification with bone lysis
9-Bilateral inferior and right middle turbinates	Right ethmoidal opacification, right sphenoidal retention cyst
10-Purulent secretion in the right middle meatus	Right maxillary opacification
11- ----------	Pansinusitis and involvement of the middle rectus of the right eye



a b

Figure 1. Fungal rhinosinusitis in patient 3: (a) preoperative and (b) postoperative CT scans.

fungal rhinosinusitis. Histological assessment showed invasion of the mucosa of the paranasal cavities in all patients who had undergone surgery. Four patients died due to the course of the hematologic disease or due to local and/or systemic dissemination of the infectious process.

After surgery, periodical endoscopic examinations were performed, during antimycotic therapy, to assure the need for revisional surgery in case of recurrence. None of our patients had the necessity to be submitted to revisional surgery. Figure 1 shows an example of the radiological findings obtained before and after surgery.

DISCUSSION

Invasive fungal rhinosinusitis can be classified based on the criteria proposed by Pinheiro et al. (1999), taking into account the immunologic status of the patient, involvement of structures adjacent to the paranasal cavity, and invasion of the mucosa and submucosa of vessels and bone tissue. Symptoms range from high fever difficult to control, which is observed in most cases (Berlinger et al., 1985; Iwen et al., 1997; Rombaux et al., 1997; Gillespie et al., 1998), to nasal discharge, ulceration of the nasal mucosa, headache and periorbital edema (Iwen et al., 1997), among others, symptoms that were also observed in the present patients.

In the present series, the most prevalent pathogen was *Aspergillus* which, as described earlier, requires a previous mucosal lesion for installation in the host, thus supporting the existence of a previous infection or of previous manipulation of the nasal cavity in these individuals. *Aspergillus* spores are normally found in mattress dust and ventilation pipes, as well as in soil and organic decomposing matter, and develop best in anaerobic environments.

Mucoraceae spores are present in dust, soil, organic decomposing matter and also in the normal nasal flora. The acid environment and high glucose concentrations observed in diabetic patients are ideal conditions for the development of this disease. Iron metabolism disorders also predispose to mucormycosis.

Infection with *Mucor* or *Aspergillus* usually develops after inhalation of their spores. Dissemination of the primary focus to other organs such as brain, liver or kidney has been observed. *Aspergillus* and *Mucor* can invade vessel walls, partic-

Table 3. Clinical-surgical treatment and evolution.

Patient	Clinical treatment	Surgical treatment	Evolution
1	Amphotericin B	Caldwell-Luc and complete left inferior turbinectomy	Died
2	Amphotericin B	Caldwell-Luc and complete left inferior turbinectomy	Cured
3	Ketoconazole	Sphenoidectomy	Cured
4	Amphotericin B	Sphenoidectomy, complete ethmoidectomy and right maxillectomy	Cured
5	Amphotericin B	Right maxillary antrostomy	Cured
6	Amphotericin B	Caldwell-Luc and complete left inferior turbinectomy	Cured
7	Fluconazole	Turbinectomy and maxillary antrostomy	Cured
8	Amphotericin B	Antrectomy, polypectomy and Caldwell-Luc	Cured
9	Amphotericin B	Bilateral middle, right inferior and complete left turbinectomy	Died
10	Amphotericin B	Caldwell-Luc and right middle turbinectomy	Died
11	Amphotericin B	Left Caldwell-Luc	Died

ularly artery walls, resulting in thrombosis, ischemia and bleeding. The incidence of invasive aspergillosis in patients with hematologic disease has been steadily increasing from 6% in the fifties to 20-30% during the last few years. This higher incidence is due to the increasingly aggressive treatment of the base hematologic disease and the use of broad-spectrum antibiotics (Pinheiro et al., 1997; Rombaux et al., 1997).

As reported by others (Berlinger et al., 1985; Waitzman et al., 1994; Iwen et al., 1997; Rombaux et al, 1997; Gillespie et al., 1998), invasive fungal rhinosinusitis mainly affects individuals with reduced cellular immunity. In the present study, neutropenia was not predominant in only one case of diabetes mellitus.

For invasive fungal rhinosinusitis, the most commonly used drugs are amphotericin B and those derived from imidazole. Nevertheless, new drugs such as caspofungin, voriconazole and ravuconazole have been recently used with great success in severe fungal diseases in imunocompromised patients. (Dupont, 2003; Kartsonis et al., 2003; Nasa et al., 2004; Petraitiene et al., 2004).

The combination of amphotericin B and radical resection of the infiltrated areas is considered to be the best treatment (Weber et al., 1987); however, we observed that the earlier the diagnosis is made, the better the prognosis. Debridement of the necrotic tissue is an urgent requirement since the fungus develops in necrotic tissue and vessel thrombosis prevents the medication from reaching the affected tissues. As a consequence, removal of the nasal turbinates, middle maxillary wall and, sometimes, part of the palate, orbital content and skin is often required depending on the extent of the infection. The sinusal approach should be based both on endoscopy and on an external access.

Early diagnosis and treatment of systemic mycosis are fundamental for these high risk patients. The diagnosis might be difficult since symptoms can be nonspecific, especially in individuals with leukopenia, fever or other associated infections. These findings have been emphasized in the literature and some authors (Iwen et al., 1997; Rombaux et al, 1997; Gillespie et al., 1998) tend to screen immunosuppressed patients by means of middle turbinate biopsy, computed tomography and fibroscopy in order to permit an early diagnosis and treatment of fungal rhinosinusitis. However, the interpretation of positive cultures might be impaired by the fact that fungi might result from air contamination or are colonizers of the upper airways.

In the present study, we observed a survival rate of 63.6%, a value higher than the average survival of 20 to 50% reported in the literature (Waitzman et al., 1994). The immediate surgical approach, together with systemic antifungal therapy, may have improved the prognosis of these patients. However, survival also depends, in part, on the recovery from factors predisposing to immunosuppression, such as bone marrow function in patients with hematologic disease.

We conclude that an early diagnosis of invasive fungal disease is very important in immunocompromised patients, and that this disease should be suspected in all patients with immunosuppressive disease presenting signs of headache, fever and associated nasosinusal symptoms. Immediate surgical treatment, combined with systemic antifungal therapy, should be instituted as early as possible to improve the prognosis of the patient.

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