Introduction

Rhinocerebral mucormycosis (RCM) is a rare opportunistic fungal infection usually encountered in immunologically incompetent patients. RCM is the most frequent syndrome of mucormycosis. It is caused by fungi of the order Mucorales; it is the most rapidly fatal fungal disease in humans, with high morbidity and mortality rates. Early diagnosis and treatment are the key elements to survival of RCM.

In this retrospective study, we report five cases of RCM diagnosed and treated in our department, and we discuss clinical presentation, diagnostic means, therapeutic modalities, and prognostic factors of this severe disease.

Materials and methods

Between 1997 and 2007, five patients were hospitalised for RCM in the department of otorhinolaryngology-head and neck surgery of the Habib Thameur Hospital in Tunis. Two of the five patients included in the present retrospective study were male, and the mean patient age was 55 years (range 24-72 years). All patients underwent medical and surgical treatment. Follow-up was clinical and radiological with a mean period of 17 months.

Results: All patients were diabetic. Exophthalmia, rhinorrhea, and ophthalmoplegia were the most frequent symptoms observed. One patient had loss of visual acuity and another exhibited peripheral facial palsy. One patient had extensive hemifacial cutaneous necrosis. Nasal endoscopy revealed black necrotic lesions in one case, and another patient had a tumefaction localised in the left middle meatus. Necrotic lesions were most often found in the orbit, the maxillary and the ethmoidal sinuses on computed tomography (four cases for each site). One patient had thrombophlebitis of the cavernous sinus, and another had an intracranial extension. All patients were administered ordinary insulin and intravenous amphotericin B. Surgical debridement of the nasal cavity and the involved sinuses was performed through lateral rhinotomy (four cases) or endoscopy (one case). Unilateral orbital exenteration was associated in two cases. Progression was favourable in four cases; one patient died from sepsis despite aggressive treatment.

Conclusion: Early diagnosis is crucial for the management of RCM. Treatment of underlying disorders, use of intravenous amphotericin B, and aggressive surgical intervention are key in reducing morbidity and mortality rates.
for one month. Surgical treatment included radical surgical debridement of the nasal cavity and sinuses after lateral rhinotomy or endoscopy. Follow-up was clinical and radiological with a mean period of 17 months (range 13-22 months).

Results

Exophthalmia (four cases) and ophthalmoplegia (two cases) were the most frequently observed ophthalmological symptoms (Table 1). One patient exhibited an associated kerato-conjunctivitis and another reported loss of visual acuity. Rhinological symptoms included rhinorrhea (three cases) and nasal obstruction (one case). Two patients reported a history of chronic headache and facial pain.

Clinical examination disclosed inflammatory hemifacial tumefaction with periorbital oedema in two cases; one of these patients possessed an associated extensive hemifacial cutaneous necrosis involving the left cheek, the nose, and the left orbit. Unilateral peripheral facial palsy was noted in one case. Nasal endoscopy identified black necrotic lesions in one case, and another patient had a tumefaction localized in the left middle meatus. Clinical data raised suspicion of mucormycosis and patients were hospitalized for biopsy and imaging.

CT with contrast media injection was performed to determine lesion localization and extent. RCM diagnosis was suspected by observation of opacifications of paranasal sinuses, as well as extensive and destructive lesions. Necrotic lesions were found most often in the maxillary and ethmoidal sinuses (four cases for each sinus). Extensive lesions to the orbit were noted in four cases, and to the infratemporal fossa in one case. One patient exhibited thrombophlebitis of the cavernous sinus, and another had an intracranial extension (Table 2; Figure 1). MRI was performed for two patients (Figure 2); it was not performed for all patients since CT with injection of contrast media adequately identified and described the lesions and their extensions for three patients. MRI showed hypointensity on T1 and heterogenous signal on T2 weighted images.

Histopathological and mycological examination confirmed diagnosis of mucormycosis.

All patients were placed under non-specific antibiotherapy (amoxicillin – clavulanic acid: 100 mg/Kg/day intravenously) for few days before confirming diagnosis of mucormycosis. Intravenous amphotericin B was added after mycological or histological confirmation of diagnosis. This treatment was replaced with fluconazole in one patient who developed transient failure of renal function. Antifungal treatment was continued for at least six weeks. All patients were also administered rapid-acting insulin to control blood glucose levels.

All patients underwent surgical debridement of the nasal cavity and the involved sinuses. Lateral rhinotomy was performed in four cases and endoscopy in one case. Unilateral orbital exenteration was associated to lateral rhinotomy in two cases.

| Table 1 |
| Clinical presentation of RCM patients (ophthalmologic, rhinologic and facial signs) |
| Clinical presentation | Number of cases (n = 5) |
| Ophthalmologic: | |
| exophthalmia | 4 |
| ophthalmoplegia | 2 |
| loss of visual acuity | 1 |
| kerato-conjunctivitis | 1 |
| Rhinologic: | |
| rhinorrhea | 3 |
| nasal obstruction | 1 |
| Facial: | |
| pain | 2 |
| tumefaction | 2 |
| periorbital oedema | 2 |
| cutaneous necrosis | 1 |
| facial palsy | 1 |

| Table 2 |
| Sites where necrotic lesions were found on computed tomography |
| Site | Number of cases (n = 5) |
| Sinuses: maxillary | 4 |
| ethmoidal | 4 |
| sphenoidal | 2 |
| frontal | 1 |
| Orbit | 4 |
| Infratemporal fossa | 1 |
| Cavernous sinus (thrombophlebitis) | 1 |
| Skin and subcutaneous tissues | 1 |
| Cranium | 1 |
Despite aggressive surgical treatment and early intravenous administration of antibiotherapy and antifungal drugs, one patient died four days after surgery from sepsis due to extensive necrotic facial cellulites. Progression was favourable in the other four cases with regression of symptoms and lesions on the CT. One patient required revision surgery because persistent sinonasal lesions were found on CT. Loss of an eye (two cases), peripheral facial palsy (one case), and a denuded nasal cavity (one case) were the major definitive functional sequelae. On the other hand, one patient with an intracerebral extension was treated by amphotericin B over four months, with favourable disease progression and no neurological sequelae.

Discussion

Mucormycosis, a rare and severe fungal infection, is caused by a group of ubiquitous, saprophytic fungi of the class Phycomycetes, order Mucorales, family Mucoraceae, most commonly from the genera Rhizopus, Rhizomucor, and Absidia. RCM is the most common syndrome, accounting for 40 to 49% of all the mucormyoses. Rhizopus is the predominant pathogen, accounting for 90% of RCM cases. Rhizopus can be found in fruits, soil, dust, and manure, and can be cultured from the oral and nasal mucosa of humans lacking clinical signs of infection. Infection usually occurs after inhalation through the nose or mouth; a skin laceration can also become an opening for mycotic entry. There is no interhuman contamination. Several clinical syndromes of mucormycosis exist: rhinocerebral, pulmonary, cutaneous, gastrointestinal, neurogenic, renal, bony, and disseminated.

RCM can affect any age group, and although cases in healthy adults have been reported, RCM generally occurs in patients with debilitating disease. Diabetes mellitus (with or without ketoacidosis) is the most common risk factor and is associated with mucormycosis in 40% to 50% of cases (100% in our series). Other risk factors include corticosteroid use or immunosuppressive therapy (5.6% to 7%), renal failure treated by haemodialysis (7 to 14%), leukaemias (5.5%), lymphomas, neutropenia, malnutrition, and desferoxamine therapy.

Patients with RCM will present with facial pain, headache, and fever. Infection can lead to proptosis, periorbital oedema, chemosis, ophthalmoplegia, and loss of vision if the orbital apex is affected (two cases in our series). Infection of the central nervous system is usually attributed to direct extension of necrotic lesions from the nose or paranasal sinuses or through vascular channels, the supraorbital fissure, or the cribriform plate (one case in our series). Endoscopy can reveal black lesions in the nasal cavities or necrotic turbinates. If the disease invades the oral cavity, a black necrotic eschar is often found in the palate. Early funduscopic examination may be normal, but haemorrhages or central retinal artery occlusion often occur as late signs. Because Mucorales often invades blood vessels, infarction, necrosis, and thrombosis are the major characteristics of this disease. Carotid artery occlusion due to fulminant RCM has been reported. RCM can also spread by perineural invasion.

CT of patients with RCM typically shows opacification of the paranasal sinuses, thickening of the sinus mucosa, and bone destruction. The most frequently affected sinuses are the ethmoid and the maxillary sinuses. CT will also reveal soft tissue swelling, proptosis, and swelling of the extraocular muscles. MRI is currently the imaging method of choice in diagnosing cavernous sinus thrombosis; MRI is also more accurate in
determining soft tissue, orbital, and intracranial extensions. In our series, cavernous sinus thrombosis was diagnosed in one patient on CT after using contrast.

Definitive diagnosis of mucormycosis can only be made by a biopsy that identifies the characteristic hyphae and by culturing the fungus. Histologically, mucormycosis is characterised by extensive tissue necrosis and the presence of numerous large fungal hyphae, which are nonseptate and have a ribbon-like appearance, with budding and dichotomous branching.

**Treatment and prognosis**

RCM is a rapidly progressive disease in which morbidity and mortality are directly related to the length of time before diagnosis and treatment. Indeed, early diagnosis of RCM increases survival substantially; Yohai et al. found that patients treated fewer than six days from the onset of symptoms had a survival rate of 76-81%. If treatment was delayed more than 12 days after symptoms began, survival dropped to 36-42%.

The initial medical approach to RCM is to treat aggressively any underlying predisposing disorders. Blood glucose levels should be controlled rigorously. Intravenous antifungal drugs should be administered as soon as diagnosis is made; wide use of amphotericin B has led to a survival rate of up to 72%. The recommended dose is 1 mg/kg daily for six weeks to three months according to the progression of the disease. Liposomal-encapsulated and lipid complex amphotericin B are newer formulations with fewer side effects that permit higher dosing. Raj et al. propose complementary treatment by local nebulised amphotericin. Proper treatment of cavernous sinus thrombosis includes appropriate antibiotic coverage and elimination of the source of infection. The use of anticoagulants is still controversial. The use of steroids is not recommended, as steroids increase the risk of extension of the infection, especially for diabetic and immunosuppressed patients.

Hyperbaric oxygen has also been used to treat RCM; some studies have demonstrated direct in vitro fungistatic activity and a reduction in tissue hypoxia, which may reverse the hypoxic acidosis that aids fungal proliferation. However, other studies revealed no significant difference in effectiveness of therapy with or without hyperbaric oxygen.

Surgical management also should be initiated early in the course of treatment, involving debridement of all infected tissues; multiple surgeries are often necessary for adequate debridement. Endoscopic, endonasal, or combined approaches are recommended, according to the extent of the lesions. Radical resection may be required in some cases of extensive lesions, including partial or total maxillectomy, partial rhinectomy, and orbital exenteration (which was performed in two of our patients). Intracerebral debridement should be performed if possible. In our series, only one patient had a cerebral extension that was judged nonoperable by neurosurgeons.

Although combined surgery and amphotericin B strategies result in a survival rate of 66.6% to 80%, 70% of survivors will encounter some type of functional deficit (two cases in our series). Loss of visual acuity, facial nerve palsy and denuded nasal cavities are the major functional and aesthetic sequelae. Findings indicating poor prognosis include intracranial involvement and extensive facial necrosis. These two factors are significantly associated with a high morbidity rate are the major causes of death for patients having RCM.

**Conclusion**

RCM is a rare and severe fungal infection occurring mainly in diabetic and immunosuppressed patients, causing rapid invasion of the paranasal sinuses, orbit, and cranium. For our patients, clinical and radiological suspicion of RCM, then early biopsy allowed early diagnosis. Treatment of underlying disorders, use of intravenous amphotericin B, and surgical intervention were the keys to improving patient outcome. However, despite this aggressive treatment, RCM remains a severe disease with high morbidity and mortality rates.

**References**

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