MUCORMYCOSIS : FOUR CASE REPORTS

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MUCORMYCOSE : A PROPOS DE QUATRE OBSERVATIONS

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RÉSUMÉ

Introduction : La mucormycose est une infection fongique rare, invasive d'évolution souvent fatale. Elle touche avec prédilection les sujets diabétiques. Le but de notre étude est de relever les caractéristiques cliniques, radiologiques, thérapeutiques et évolutives de mucormycose.

Méthodes : Il s'agit d'une étude rétrospective portant sur des observations de mucormycose colligés dans le service des maladies infectieuses de l'hôpital La Rabta entre Janvier 1988 et Décembre 2004. Le diagnostic de mucormycose a été confirmé par les examens mycologiques et/ou anatomopathologiques.

Résultats : Nous rapportons quatre observations survenues chez des diabétiques (3 hommes et 1 femme). Trois étaient en acido-cétose au moment du diagnostic. L'atteinte rhino-cérébrale a été observée chez deux patients et la localisation naso-sinusienne chez les deux autres patients. Le diagnostic a été confirmé par l'examen mycologique et/ou histologique. Le traitement est basé sur l'amphotéricine B par voie systémique, associée au débridement chirurgical des lésions. L'évolution était fatale chez deux patients.

Conclusion : La mucormycose est une infection grave chez les sujets diabétiques. Le pronostic dépend très largement de la précocité du diagnostic et de la mise en route du traitement.

MOTS-CLÉS

Mucormycose, diabète sucré, Rhizopus, traitement.

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SUMMARY

Introduction : Mucormycosis is a rare and invasive fungal infection, but frequently fatal when it occurs. It commonly affects patients with diabetes mellitus. The aim of this study is to assess the clinical presentation, radiological findings, management and prognosis of mucormycosis.

Methods : this retrospective study was conducted in the department of infectious diseases of Rabta hospital between January 1988 and December 2004 and included patients hospitalized for mucormycosis confirmed by mycological and/or histological findings.

Results : the study is about four diabetic patients with mucormycosis (3 men and a woman). Three of them had diabetic ketoacidosis at the time of diagnosis. The infection was sinusal in 2 cases and rhinocerebral in the the other two cases. Treatment consisted in systemic amphotericin B combined with surgical debridement in 3 cases. A fatal outcome was noted in 2 cases.

Conclusion : Mucormycosis remains a severe infectious disease in diabetic patients. Early diagnosis and treatment is mandatory for a successful management of this infection.

KEY-WORDS

Mucormycosis, diabetes mellitus, Rhizopus, therapy.

الفطار الأشتي : دراسة حول 4 حالات

الباحثون : لـ .العماري، يـ .الكيلاني، ح . تيويري، ف .كانون، أ .غبتطني، أ .منيف، قـ .زويتن، أ .شاكر، تـ .بن شعبان.

الفطار الأشتي هو أخمجاج فطري نادر تطوره قاتل و يصيب بالخصوص مرضى السكر. تتناول دراستنا التي تشتمل على 4 حالات الخصائص السريرية و التصويرية و العلاجية و التطورية لهذه الإصابة. كل المرضى كانوا مصابين بداء السكري و كان التشخيص في كل الحالات بواسطة التحاليل الفطارية أو التشريحية المرضية. أما العلاج فهو يرتكز أساسا على " الأمفوتيريسين ب " نؤكد في الختام على أن إنذار هذه الإصابة سيء (سجلنا حالتي وفاة من الأربعة) و يتأثر بصفة ملحوظة بسرعة التشخيص و بداية العلاج.

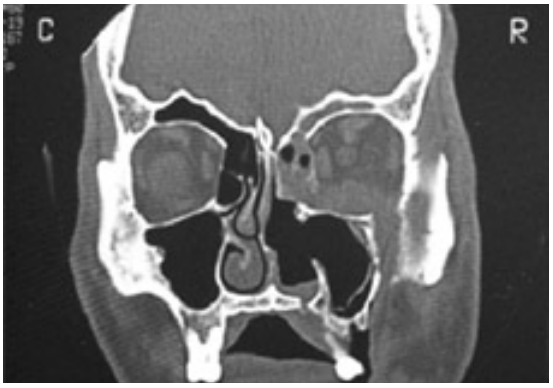
الكلمات الأساسية : فطار أشني، سكري، علاج.

Mucormycosis (Zygomycosis) is caused by several fungal species in the order Mucorales which are commonly found in soil and among decaying vegetation (1).
The three most commonly encountered species in human mucormycosis are: Rhizopus, Mucor and Absidia (2).It is an invasive fungal infection and often lethal disease which occurs in immunocompromised hosts (3). This infection affects patients with at least one of the following immunocompromising states: haematologic malignancy, corticosteroid or immunosuppressive therapy, diabetes mellitus with or without ketoacidosis, organ transplantation, deferoxamine therapy, severe burns, trauma and malnutrition in children. Immunocompetent patients rarely develop mucormycosis (3, 4). We conducted a retrospective study of four patients with mucormycosis, admitted to the Department of Infectious Diseases between 1988 and 2004.

CASE REPORTS

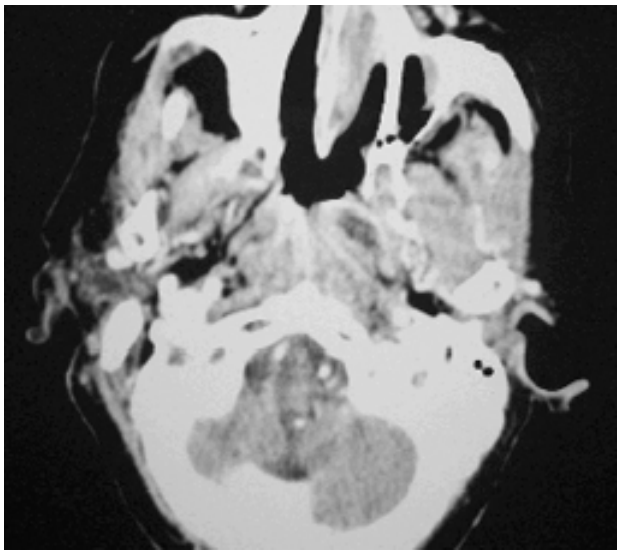
Case report N°1 : A 41-year-old man with diabetes mellitus presented with a two-week history of right facial and periorbital swelling associated with right peripheral seventh cranial nerve palsy. There was no fever. Diabetic ketoacidosis was present on admission. CT scan examination showed a right ethmoid and maxillary sinusitis with bone erosion of the ethmoid and posterior wall of the orbit. A right temporal abscess with a large soft-tissue mass in the retroorbital area was noted (Fig.1). Surgical debridement of the ethmoid sinuses and right middle turbinates was performed with incision of the temporal abscess. Histological findings were consistent with mucormycosis. Rhizopus oryzae were identified in tissue specimen culture. Treatment with amphotericin B (50mg/day) was prescribed. Two months later, CT scan examination revealed a retroorbital abscess without temporal lobe involvement and bone erosion of the right orbit floor. Debridement of the ethmoidal and sphenoidal sinuses was performed with excision of the orbital apex. Amphotericin B was given for 98 days with a total dose of 3 g. The patient was admitted to hospital 31 months after discharge with a history of purulent rhinorrhea without neurological impairment. A right hemimaxillectomy was offered to the patient who refused it. The patient is still alive with facial paralysis as a sequela.

Figure n°1 : Coronal CT image : bone erosion of the posterior wall of the right orbit associated to an abnormal infiltration of the right orbital fat.



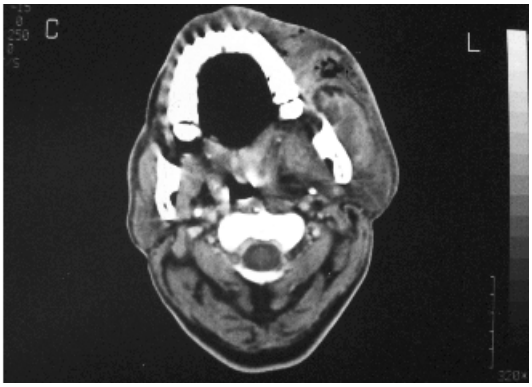
Case report N° 2 : A 66-year-old woman with an 18-year history of diabetes mellitus presented with a 13 days history of left facial edema, headache, periorbital swelling, and fever. Palatal necrosis was noted. The patient had neither ketosis nor acidosis. Aspiration of nasal fluid revealed large non-septated fungal hyphae at direct examination, and Rhizopus oryzae grew at culture. Facial CT scan examination revealed maxillary, sphenoidal and ethmoidal sinusitis, with extension towards the soft tissues. An abscess of the left parapharyngeal space without bone erosion was noted (Fig.2). Amphotericin B therapy (50 mg/day) was initiated but the patient's condition deteriorated and he died 6 days later of acute renal failure.

Figure n°2 : Axial CT image with contrast : left parapharyngeal abscess (arrow).



Case report N° 3 : A 53-year-old man presented with a 10-day history of left facial edema, periorbital swelling, and fever. His past medical history was unremarkable. He had left periorbital cellulitis and ophtalmoplegia. Edema was maximal over the left cheek with abscess.Diabetic ketoacidosis was discovered on admission. Initially, the patient was treated with antibiotics (cefazolin, gentamicin and metronidazol). Nasal endoscopic examination showed a purulent fluid without nasal necrosis. On the 5th hospital day, incision of the cheek abscess was performed yielding necrotic tissues. Fungal hyphae were identified on direct examination and Rhizopus oryzae grew at culture.Cutaneous biopsy of the left cheek showed inflammatory tissue reaction with wide fungal hyphae which were non-septated, branched at right angles, and which looked empty on haematoxylin and eosin staining.CT scanning revealed left maxillary sinusitis with bone erosion, abscess of the cheek without cerebral involvement (Fig.3).Six days onset of treatment, a necrotic eschar developed with extension to the whole cheek, and the patient died.

Figure n°3 : Axial CT image with contrast: heterogeneous infiltration of the left mandibular angle compatible with a cheek's abscess (arrow).



Case report N° 4 : A 52-year-old man with a 12-year history of diabetes mellitus was admitted with a 30-day history of left facial pain with fever appearing after dental extraction. On admission, he was also complaining of palsy of the 7th and 6th cranial nerves and of facial numbness. A fistula on the left side of the palate wi th nasal necrosis was noted. Facial CT scanning showed soft tissue infiltrates of maxillary space with extension to the left pterygopalatin fossa and infratemporal fossa. Bone erosion was noted involving the posterolateral wall of the left maxillary sinuses, the floor of the orbit, the greater wing of the sphenoid and middle turbinate without orbital or cerebral involvement. Facial MRI with gadolinium revealed intracranial extension with stenosis of the internal carotid artery at the intra-cavernous portio (Fig.4 and 5).There was a meningeal enhancement at the left temporal fossa without orbital involvement. Initially, the patient was treated with antibiotics (cefotaxime, gentamicin and metronidazol) without improvement. Surgical debridement of necrotic tissue and of the left middle turbinate was carried out. Histological findings were consistent with mucormycosis. However, the culture failed to grow. Amphotericin B was given for 222 days with a total dose of 5 g and the patient was then discharged in a stable condition.

Figure n°4 : Coronal T1-weighted MRI image with contrast : enhancement of the internal carotid artery at intra-cavernous portio (arrow) associated to meningeal enhancement at left temporal fossa.

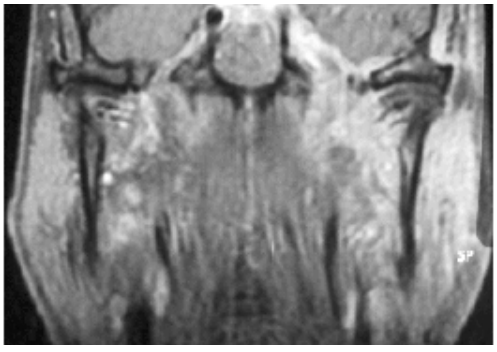
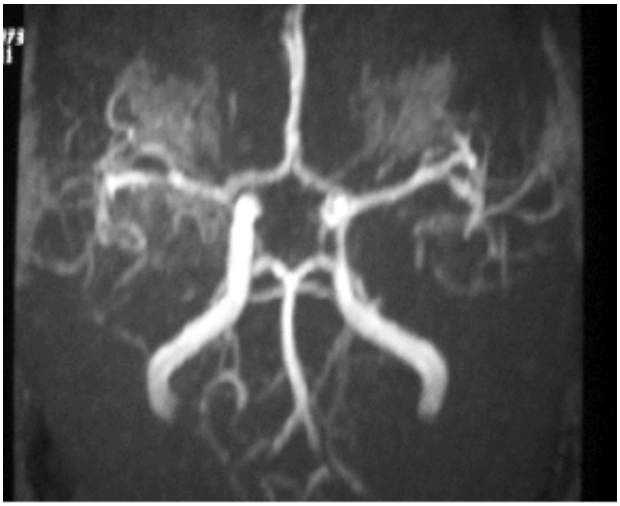


Figure n°5 : Angio-MRI: stenosis of the internal carotid artery (arrow).



DISCUSSION

The first case of mucormycosis was described in 1885 by Paltauf, who coined the term mycosis mucorina. In 1943, three cases of rhinocerebral mucormycosis were reported in diabetic patients (1). The most pathogenic species are members of the family Mucoraceae. Rhizopus oryzae is the predominant pathogen and accounts for 60% of all forms and 90% of rhinocerebral cases (1, 4).The presenting symptoms and signs are often subtle. All species of mucorales produce similar clinical features. The clinical presentation is divided into at least six syndromes: rhinocerebral, pulmonary, cutaneous, gastrointestinal, central nerve system, disseminated, and miscellaneous (3, 5). Certain risk factors seem to be more commonly associated with specific presentations. For example, patients who have diabetic ketoacidosis typically develop rhinocerebral mucormycosis. Leukemic patients who are neutropenic are most likely to develop pulmonary involvement, whereas children with kwashiorkor typically present with gastrointestinal mucormycosis. Rhino-orbital-cerebral mucormycosis (ROCM) is the most common form of infection (44 - 49%) with a strong association with poorly controlled diabetes mellitus (3, 5). As for our patients, rhino-cerebral form of infection occurred in two patients with diabetes mellitus. The exact mechanism of increased susceptibility of diabetics remains unknown. However, Rhizopus organisms have an active ketone reductase system and thrive in high glucose, acidotic environment (1). Infection occurs following inhalation of spores of mucorales into the oral and nasal mucosa. Ingestion or contamination of wounds with these fungi is possible (2). Generally the infection starts in the nasal tissues and spreads by direct extension into paranasal sinuses and then to the orbit. Intracranial extension occurs via blood way or more commonly by direct extension through the superior orbital vein, superior orbital fissure, or the cribriform plate (6). For our patients, the infection began in the paranasal sinuses and progressed to the orbit or the brain, if undiagnosed. The internal carotid artery

and cavernous sinus are commonly occluded, as in case 4. Furthermore, perineural invasion was noted in 90% of biopsies, may explain the rhino-orbital-cerebral involvement. These data are of importance in the differential diagnosis of mucormycosis (2, 3, 6). Therefore, the only way to make a definitive diagnosis of this disease is by visualizing the characteristic hyphae in sections of tissue and by growing the fungus in culture. Mucorales appear as irregularly shaped, broad (10-50μm), aseptate hyphae with right-angle branching. Rhizopus accounted for 70% of culture-positive cases in one review (6). It was the causative agent in three cases in our report. Neuroimaging (CT scan and MRI) are helpful for establishing orbital and intracranial involvement (7). Extensive debridement, amphotericin B at the dose of 1-1.5 mg/kg a day, and treatment of the patient's underlying illness are the basis of the recommended therapeutic procedure. Amphotericin B and its formulations remain the agents of choice for the treatment of mucormycosis and until recently, have been the only drugs clinically active in vitro against zygomycetes (8). Many new broad-spectrum triazole agents have been reported to be active against zygomycetes such as posaconazole and ravuconazole. Posaconazole has recently been shown to be effective against zygomycetes in vitro and in animals models (8,9). It is promising as an effective therapy against Rhizopus spp. This drug has been successfully used as salvatage therapy in patients with refactory zygomycoses or those intolerant of amphotericin B treatment (10). However, its role, whether as a single agent, or in combination with amphotericin B in the primary treatment of zygomycosis requires further assessment (3, 9, 10). Moreover, treatment with hyperbaric oxygen should also be considered. It is thought to exert a direct fungistatic effect, decrease tissue hypoxia and tissue acidosis (6). However, the prognosis remains poor with high mortality ranging between 30 and 69 %(3, 6).

CONCLUSION

Mucormycosis remains a severe infectious disease in diabetic patients and it is characterized by a high mortality rate. Clinical diagnosis is often difficult and delayed. Aggressive diagnostic procedures for histo-microbiological studies are required to confirm this disease. Early diagnosis with combined medical and surgical treatment is necessary to improve the outcome.

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