Naso-Orbital-Cerebral Mucormycosis Case Report of Surgical Management

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Abstract

Mucormycosis is a rare, aggressive opportunistic infection from a fungus of the order of mucorales. This infection is usually seen in patients with underlying conditions such as diabetes mellitus and haematological malignancies. This infection could be presented in various clinical forms, but Rhino-Orbito-Cerebral Mucormycosis (ROCM) is the most common. In this article we report a case of a middle age man suffered from poorly controlled diabetes and Leukaemia. He started with an atypical clinical form of ROCM, attending to the Emergency room with a progressive right eye acute orbital apex syndrome (OAS) which quickly evolves to a bilateral affection. After clinical and endoscopic exhaustive examination and radiologic imaging were done, a high suspect of ROCM was established. An aggressive surgical debridement of necrotic tissue and reservoir were done, bilateral orbital exenteration and an aggressive antifungal intravenous and local treatment were done. The man is successfully free of infection at this moment.

ABBREVIATIONS

ROCM: Rhino-Orbito-Cerebral Mucormycosis; OAS: Orbital Apex Syndrome; TC-Scan: Computed Tomography Scan; MRI: Magnetic Resonance Image; ENT Specialist: Ear Nose Throat Specialist

INTRODUCTION

Mucormycosis or zygomycosis is a rare opportunistic, life-threatening infection resulted from a fungus of the order mucorales (subphylum Mucormycotina). This infection is characterized by a rapid progression among the tissues, angi-invasion and high mortality, and represents the third most common fungal infection after candidiasis and aspergillosis [1-5]. At present, the incidence of Mucormycosis appears to be increasing in The United States and Europe due to the rise of risk factors [1,3,5]. Among 5 subtypes (rhino-orbito-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated), rhino-orbito-cerebral Mucormycosis (ROCM) is the most common clinical form of the disease (40%) [1,2,5]. The patient's underlying medical condition that predispose to this infection are diabetes mellitus, especially ketoacidosis, immunosuppressive conditions, neutropenia, malnutrition, burns, severe trauma, renal failure and long-term steroid or immunosuppressive therapy [1,3,5-7]. In this article, we report a case of a successfully treated ROCM in an immune suppressed and diabetic patient. After an atypical initial presentation, the patient evolved into an Orbital Apex Syndrome (OAS). We present the clinical evolution of this case and its successful surgical and medical treatment.

CASE REPORT

A 61-year-old male with type 2 diabetes and chronic lymphocytic leukemia presented to ENT Emergency department with a nonspecific fronto-facial headache. The patient suffered from fronto-facial headache that interfered night rest since 2 weeks, right palpebral ptosis and right facial hemihypesthesia. There was no history of fever, purulent nasal discharge or foul odour. He had been misdiagnosed with an acute sinusitis and treated with Levofloxacin, Clarithromycin and corticosteroid therapy for 10 days. In his medical history we must remark that he was diagnosed with B-Cell Chronic Lymphocytic Leukaemia in 2008 and had been treated with different lines of chemotherapy since then, presenting lymphopenia due to these treatments. The patient was also being treated with metformin for his type 2 diabetes presenting an average blood sugar level of 260mg/dl at the admission time. He also had chronic obstructive pulmonary disease, hyper uricemia and renal lithiasis. In the physical examination his overall status was good despite the pain, he presented right palpebral ptosis, right facial hemi hypesthesia, isochoric and reactive pupils, no diplopia, normal ocular fundus and visual acuity test was correct.
Exploration of nasal cavity was normal, presenting a pale mucosa without necrotic regions or nasal discharge. The biochemical blood analysis presented an elevated Reactive C Protein, 265 mg/dl blood sugar level and lymphopenia (lymphocytes 0.42*10³/uL, 4.2%). The computed tomography scan (CT-scan) of the paranasal sinuses revealed changes in the periorbital fat tissue as well as right maxillary, sphenoidal and ethmoidal sinusitis without any specific lesions suggesting rhino-orbital mucormycosis. (Figure 1). The patient was hospitalized and during his stay presented clinical worsening with pain, a significantly decrease of right ocular motility, right palpebral swelling, proptosis and reduction of visual sharpness. Ophthalmologic right eye examination revealed no light perception and ophthalmoplegia with impairment of cranial nerves II,III,IV,V and VI culminating in a diagnosis of an OAS. Meanwhile he presented initial symptoms of an OAS (evolving from palpebral swelling and proptosis to loss of vision, are active mydriasis and funduscopic imaging of a retinal detachment) also in the contralateral eye. During his stay he presented apoor control of blood glucose levels. No necrotic ulcers in the craniofacial area were noticed. In following blood analysis he presented pancytopenia requiring a supplementary Immunoglobulin therapy. At this stage of the illness and with the aim of making a complete differential diagnosis of the bilateral acute OAS, several imaging tests such as CT scan and magnetic resonance image (MRI) were performed. They described extension of the inflammatory changes to the right pterygopalatine fossa, orbital apex and bilateral paranasal sinuses (Figure 2). In the last MRI exam he presented a 9mm right fronto basal image suggestive of cranial progression of Mucormycosis (Figure 3).

For the definitive diagnosis a biopsy of the maxillary sinus and orbit was performed. The histopathological examination identified non-septate mucormycotic hyphae. The culture report was positive for mucorales fungi and negative for anaerobics. The patient required aggressive surgical treatment consisting of nasal endoscopic surgery, bilateral orbital exenteration and bilateral Cadwell-Luc. The patient underwent aggressive endoscopic removal of the involved tissue (inferior nasal turbinates, affected nasal and paranasal sinuses mucosa, drainage of bilateral maxillary, frontal and sphenoidal sinuses). In order to eliminate the main reservoir of the fungal infection a removing of the posterior wall of maxillary sinus and drainage of the pterygopalatine fossa was executed (Figure 4,5). The antimicrobial treatment he received during the hospitalization period (pre and post-surgery) was: intravenous liposomal amphotericin b (2 mg/kg/24h increasing dosis to 5 g/kg/24h and 10 mg/kg/24h suspecting intra cranial progression) and Caspofungin (interrupted because of cholestasis) and piperazilin/tazobactam (interrupted after the culture report). Both orbital cavities and nasal sinuses were irrigated with amphotericin b deoxycholate diluted in glucose serum at 5% intra operatively and post-surgically once a day. After the treatment period, the patient was discharged from the hospital with Domiciliary Hospitalization Program to continue the intravenous administration of amphotericin to complete 42 days therapy. After wards he will be treated with oral posaconazol. After two months since diagnosis and surgical and medical aggressive treatment, the patient medical condition is favourable with resolution of acute symptoms and free of intracranial
Central mortality rate of 65% in some series [3,5]. According to Roden presented as the most fatal factor in many articles arising a intravenous drug use [1,3,5,6]. Haematological malignancy is deferoxamine therapy, burns, trauma, malnutrition and bone marrow and peripheral blood stem cell transplantation, and 2 with or without ketoacidosis, solid organ transplantation, pharmacologic immunosuppression, diabetes mellitus type 1 and 2 with or without ketoacidosis, solid organ transplantation, bone marrow and peripheral blood stem cell transplantation, deferoxamine therapy, burns, trauma, malnutrition and intravenous drug use [1,3,5,6]. Haematological malignancy is presented as the most fatal factor in many articles arising a mortality rate of 65% in some series [3,5]. According to Roden [5], et al, the most common underlying condition for mucormycosis in the oral, nasal, paranasal sinuses and maxillofacial areas is diabetes mellitus. They published a review of 929 patients with zygomycosis between 1885 and 2005. Sinuses were the most frequent site of infection 39% followed by pulmonary 24% and cutaneous types 19%. Rhinocerebral disease was seeing more frequently in patients with diabetes (33%). The case we report is a patient who suffered from diabetes mellitus type 2 and a haematological malignancy.

Mucormycosis is an invasive fungal infection, which exhibits a remarkable affinity for arteries and veins producing an angioinvasion of the wall of the blood vessels, causing mechanical and toxic damage to the intima leading to thrombosis, invading later on the lymphatics and veins. These thrombosis cause emboli and vascular obstruction responsible for tissue necrosis [8]. The infection progressively spreads from the nasal mucosa and paranasal sinuses to the palate, orbits and brain, what could promptly result in cavernous sinus, carotid artery or jugular vein thrombosis. There is a large variety of symptoms that mucormycosis can produce: sinusitis, nasal obstruction, purulent nasal discharge, facial numbness, headache, fever and epistaxis are the most common initial symptoms, since this infection usually began in the palate or paranasal sinuses [2,8].

Appearing of a necrotic eschar in naso facial and palate area is a characteristic sign that is not always present. The orbital involvement is related to the vascular tropism of the fungus which induces vessels thrombosis, mechanical and toxic damage and subsequent tissue necrosis [2,6,8]. The affection is usually unilateral and is characterized with these symptoms: orbital pain, diplopia, ophthalmoplegia, periorbital edema, chemosis, exophthalmia or even blindness. The eye fundus examination is a key for the diagnosis of ROCM presenting as an OAS. It may reveal a venous congestion or thrombosis of the artery or of the central vein of retina [2,6,8]. In the absence of characteristic mucormycosis indicators such us thrombosis and necrotic eschar it can be a difficult entity to diagnose. Thurtell, et al [9] reported 14 patients with a positive biopsy for ROCM and presenting OAS, with only one patient being correctly diagnosed at presentation. OAS is an acute and threatening syndrome with retro-orbital pain, complete ophthalmoplegia and visual loss. When any sinus disease with OAS is observed in a diabetic or immunocompromised patient even clinically suspect or by CT or MRI, a fungal etiology should be suspected. Image testing are effective techniques in diagnosing OAS, but the most reliable is the biopsy [4]. The case we report present a nonspecific 2 weeks headache, accompanied of initial OAS symptoms in the right ear but without any necrotic areas or nasal discharge. In order to make a complete differential diagnosis, several image testing were performed. The match of the clinical evolution and the last MRI images results in a high suspected ROCM as the first diagnosis option. Nonetheless, the final diagnosis cannot be held without a biopsy. There are four factors which describe a successful treatment: a prompt diagnosis, reversal of the underlying predisposing factors, early, aggressive and appropriate surgical treatment based on the debridement of infected tissue and reservoir, and appropriate antifungal and medical treatment [6,7,10]. The first factor, an early diagnosis, is imperative and can hugely reduce the patient’s mortality and morbidity. The second one, reversal of underlying risk factors, is of high relevance. Finally, a combination of radical surgical debridement and intravenous and local liposomal amphotericin

**Figure 4** Endoscopic guided surgical aggressive debridement of necrotic tissue and removal of the posterior wall of maxillary sinus, draining the pterygopalatine fossa.

**Figure 5** Bilateral orbital exenteration.

lesions. The patient is being controlled by Ear, Nose and Throat specialist, Infectious disease physician, maxillofacial surgeon, Haematologist, Endocrinologist, Rehabilitation specialist and a psychiatrist.

**DISCUSSION**

Rhino-orbito-cerebral mucormycosis (ROCM) is a severe opportunistic fungal infection. This infection is characterized by rapid progression and high mortality, and represents the third most common fungal infection after candidiasis and aspergillosis. At the moment, the incidence of fungal infections is rising due to increased incidence of diabetes and use of immunosuppressive agents [1,3,5]. Mortality rate of mucormycosis has remained ≥ 40 % for the last decades, in spite of an aggressive treatment based on surgical debridement with or without exenteration and antifungal therapy [1,3,5]. The major risk factors for mucormycosis are: haematological malignancy, neutropenia, pharmacologic immunosuppression, diabetes mellitus type 1 and 2 with or without ketoacidosis, solid organ transplantation, bone marrow and peripheral blood stem cell transplantation, deferoxamine therapy, burns, trauma, malnutrition and intravenous drug use [1,3,5,6]. Haematological malignancy is presented as the most fatal factor in many articles arising a mortality rate of 65% in some series [3,5]. According to Roden [5], et al, the most common underlying condition for mucormycosis in the oral, nasal, paranasal sinuses and maxillofacial areas is
B therapy must be done [10,11]. In fact, an aggressive surgical treatment itself is known to increase the survival rate[5]. Fungi thrive in necrotic tissue, that is why debridement is necessary and should be carried out well close to the bleeding periphery, as the drug may not effectively distributed in thrombosed vessels [8]. According to Seiff, et al., [12], the pterigopalatine fossa through the sphenopalatine foramen is the main reservoir for Mucor, and acts as the main pipe for the spread of infection. This is the main reason why it is a good practice to remove the posterior wall of the maxillary sinus, in order to expose the pterigopalatal fossa [7]. In order to eliminate any fungal reservoir and avoid an intracranial invasion, in patients with progressive orbital affection an aggressive surgical debridement with an orbital exenteration is advised. According to Plowes, et al., [7], patients with the same symptoms and the same risk factors, being exenterated have a higher survival rate. Never the less, orbital exenteration is always a controversial decision. No standard of care currently exists to guide specialists on when exenteration may benefit a mucormycosis patient.

In the case we report, we decided the bilateral orbital exenteration accompanied with the debridement of the pterigopalatine fossa and orbital superior fissure necrotic tissue due to the suspect of intracranial progression of the illness (Figure 3) and the bilateral progressive orbital apex syndrome [7,13]. As far as the correct medical treatment in a ROCM, the most standard management includes an intravenous and local irrigation of liposomal amphoteribin B [11]. Liposomal amphoteribin B has similar or better survival results than amphoteribin B with less adverse effects, such as nephrotoxicity [3,8,13]. Recently studies have demonstrated that liposomal amphoteribin B, fluconazole and caspofungin can be combined with each other, obtaining successful outcomes. Due to vascular thrombosis risk, anticoagulation therapy is recommended in these patients [7]. An optimal and successful therapy requires a multidisciplinary collaboration of ENT/Head and Neck surgeons, Ophthalmology Specialists, Internists, Haematologist and Infectious disease specialists.

CONCLUSION

In all diabetic and immune supressed patients who come to our emergency room with an ophthalmological condition suspicious of being an OAS, the Rhino-orbital Mucormycosis must be taken into account in the differential diagnosis. An early diagnosis is crucial, reducing the morbidity and mortality of this affection. That is why a complete physical examination, endoscopic evaluation and radiological and microbiological studies must be done. If the ROCM diagnosis is confirmed, a prompt and aggressive surgical debridement of the necrotic tissue and reservoir will be the correct treatment, accompanied with an antifungal treatment, usually with intravenous and locally irrigated liposomal amphotericin b. The exenteration is still a controversial decision, which needs more prospective studies to set out the most successful procedures that must be done in these cases in order to increase the survival rates. Last but not least, reversal of the underlying predisposing factors is vital for increasing survival rates and decrease recurrences.

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REFERENCES