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CASE REPORT

Does affect combination of surgery with anti-fungal therapy prolong life a mucormycosis of sino-nasal? A Case Report

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Abstract

Acute invasive fungal rhinosinusitis (AIFRS) is a rapidly progressive disease, which usually develops in patients with uncontrolled diabetes mellitus (DM) and those thatare immuno compromised.Mucor, Rhizopus, Absidia, Rhizomucor, and other mucorales fungi that belong to thedivision Zygomycota, or Aspergillus species that belong to the division Ascomycota, may be responsible for this disease. AIFRS exhibits high rates of mortality and morbidity, and prognosis of the disease mandates early diagnosis and treatment. Treatment includes immediate surgical intervention, systemic antifungal therapy, and quick treatment of the underlying systemic disease. Before the advent of amphotericin- B, mortality rates were as high as 90 percent. However, they have been reduced to 15 to 50 percent with the combined use of surgery and amphotericin-B. In this report, we present a case of mucormycosis of the rhino-orbital area treated with endoscopic sinus surgery, a medial maxillectomy with incomplete excision of the palate, and liposomal amphotericin B.

The aim of this case report is to show that early surgery with medical therapy and regular follow-up could decrease mortality and increase life expectancy.

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Introduction

The Acute invasive fungal rhinosinusitis (AIFRS) is a rapidly progressive disease, which usually develops in patients with uncontrolled diabetes mellitus (DM) and immunocompromised patients [1]. Mucormycosis is the term most often used to describe this disease due to Mucor species in recent years.

Mucor, Rhizopus, Absidia, Rhizomucor, and other mucorales fungi that belong to the division Zygomycota, or Aspergillus species that belong to the division Ascomycota, may be responsible for this disease [2]. Mucormycosis is rare, and usually occurs in diabetic ketoacidosis, under neutropenic conditions such as hematological cancer, or in immunocompromised patients due to receiving broad-spectrum antibiotics or immunosuppressive agents, including oral or intravenous steroids and tumor necrosis factor (TNF)–alpha blockers [2]. Because of its rarity, mucormycosis is difficult to calculate accurately; further, since mucormycosis is not a reportable disease, the true incidence is unknown, but an estimated 500 cases occur in the United States (US) annually [3]. A review of mucormycosis cases at one US cancer center found that 0.7% of patients had mucormycosis at autopsy, and that 20 patients per 100,000 admissions had the disease [4].

These organisms are found saprophytically in decomposed substances, soil, and fruits, and in the throats, nasal cavities, and feces of healthy individuals; however, they may become pathogenic in immunocompromised and uncontrolled diabetic patients. High glucose levels in diabetic patients facilitate tissue invasion. Additionally, the ketone reductase system of the fungi assists with adaptation to the environment, and impairs the phagocytic function of polymorphonuclear leukocytes [5]. These organisms may proliferate in paranasal sinuses and cause thrombosis, as well as ischemic necrosis of the tissues by the involved blood vessels. They can rapidly spread and invade the eye and the brain [6]. Based on anatomical localization, mucormycosis can be classified as rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations [7].

There have been incidences of granular, sero-hemorrhagic rhinorrhea, necrotic avascular and black crusts, and septal or palatal perforation in the rhinological findings. If the eyes are involved, diplopia and loss of visual acuity may develop. Headache, lethargy, and cranial nerve symptoms indicate intracranial involvement [8].

The diagnostic criteria for AIFRS include the presence of rapidly progressing sinusitis confirmed by clinical and radiological examination, and typical endoscopic findings such as purple-black crusting, necrosis, “pale” mucosal areas and, sometimes, observation of hyphae. An accurate diagnosis is established by the histopathological demonstration of hyphal forms in the mucosa, submucosa, blood vessels, or bones of the sinuses, and cultures of biopsy material [1].

Mucormycosis results in high rates of mortality and morbidity; while a positive prognosis of the disease mandates early diagnosis and treatment. Successful treatment includes immediate surgical intervention, in addition to systemic antifungal therapy, and the rapid treatment of any underlying systemic disease. Mortality rates reached as high as 90 percent before the advent of amphotericin-B; however, they have been reduced to 15 to 50 percent with the combined use of surgery and amphotericin-B. Currently, endoscopic surgical procedures are often used, and could provide lower morbidity with comparable survival rates [8-9].

In this report, we present a case of rhino-orbital mucormycosis treated functionally with endoscopic sinus surgery, a medial maxillectomy with incomplete excision of the palate, and liposomal amphotericin-B. The aim of this case report is to reveal that early surgery with medical therapy, and regular follow-up, could decrease mortality and increase life expectancy in these cases.

Case Report

In A 67-year-old patient was admitted to the Dicle University Medical hospital on the 13th of November, 2012, with swelling around the right eye, restriction of eye movements, proptosis, nasal obstruction, a severe headache, and a poor general condition. The patient had no antecedent history of orbital symptoms; however, the initial examination revealed marked right orbital edema, hyperemia, and proptosis. An endoscopic rhinoscopic examination revealed pale, well-defined, soft, multiple greenish polypoid masses surrounded by blackish wolves, with congestion and edematous mucosa, and dark and sticky mucoid discharge in the right nasal cavity. Additionally, there was necrosis in the base of the nasal cavities and right palate, as well as bilateral hypertrophy of the turbinates of the nasal cavity (Figure 1) and post-nasal discharge. The patient was under dialysis treatment for kidney failure and had a history of diabetes mellitus. His blood glucose level was 226, urea was 143, creatinine was 5.2, Hb was 8.5, WBC was 7.3, and K was 3.4. An ocular examination revealed marked right proptosis with an associated severe impairment of visual acuity (6/10) and loss of color vision. Eye movements, especially in view of the medial lesion, were slightly restricted (Figure 2). A fundoscopy revealed papilledema and vascular changes.

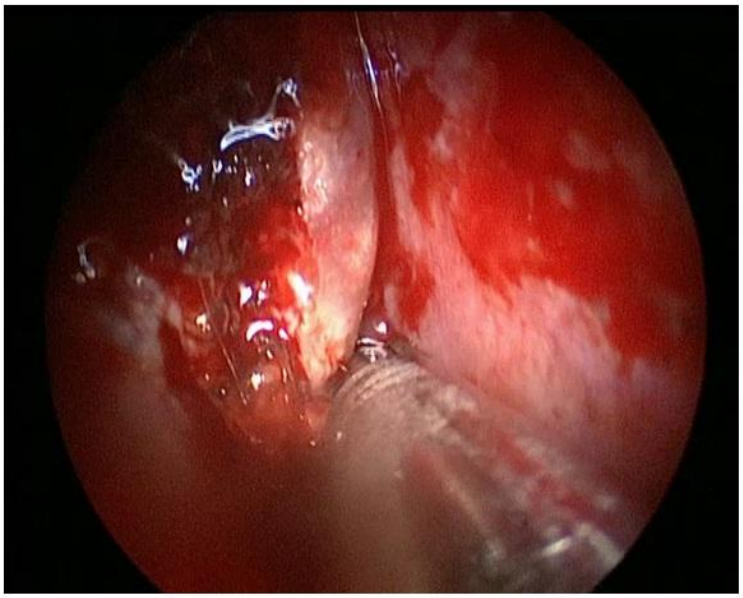

Figure 1. There were asymmetric view of ocular globes due to restriction of eye movements in the examination of patient.

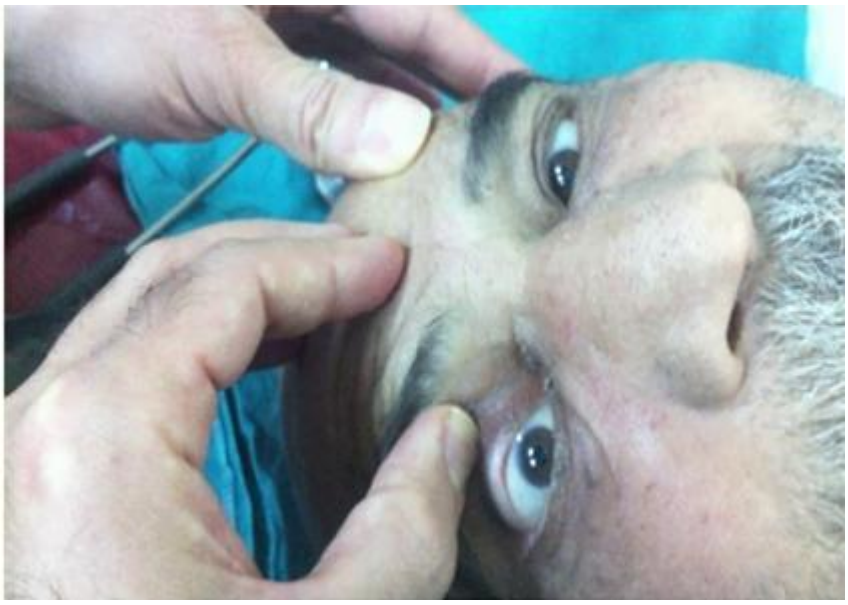

Figure 2. Endoscopic view of the nasal mucosa at the beginning of the operation.

Computerized tomography (CT) using a 64-detector CT device (Philips Medical Systems, Cleveland, OH, USA) revealed different degrees of mucosal thickening with a soft tissue density in the right nasal cavity, maxillary sinus, ethmoid cell lines, and in the infraorbital and infratemporal regions. Additionally, there was erosion in the front, posterior, and medial walls of the right maxillary sinus bone (Figure 3A). There were intensities at the level of the right maxillary sinus, nasal cavity, and inferior turbinates in the unenhanced and contrast-enhanced MR images of the corona (Figure 3B), and there was significant necrosis in the non-enhancing areas. The patient was preliminarily diagnosed with complicated fungal rhinosinusitis, confirmed as compatible with the existing clinical history, physical examination, and preoperative imaging (Figure 3A-B), uncontrolled diabetes mellitus (DM), and immunocompromised patients with renal failure.

We chose a multidisciplinary approach for this patient, with the regulation and support of the metabolic system and the patient's other conditions prior to surgery. We performed a functional endoscopic sinus surgery with a medial maxillectomy and excision of the right palatum on the second day after admission to the hospital. During surgery, we excised and cleaned the nasal polypoid masses and necrotic tissues filling the right nasal passage, the maxillary sinus, and the ethmoid cells until the posterior ethmoid sinus and lateral maxillary sinus were bloody. We also excised the right half of the palate due to necrosis in the base of the nasal region up to the palate.

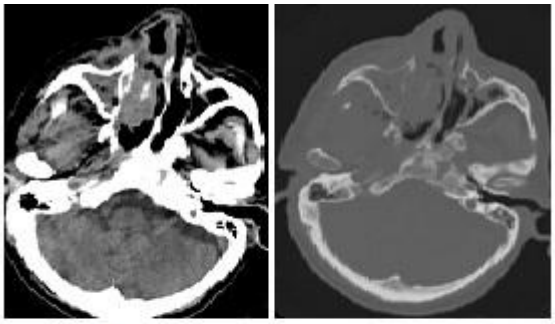

Figure 3 A.

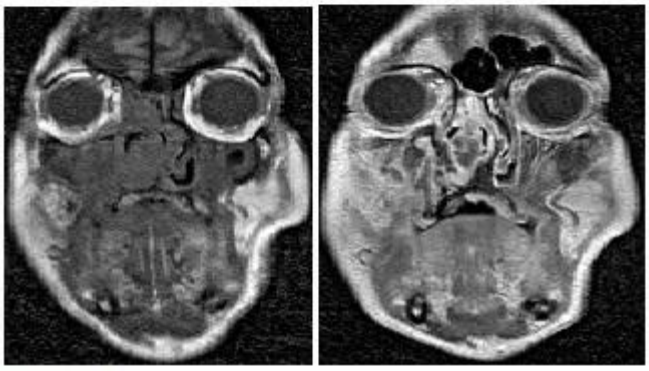

Figure 3 B:

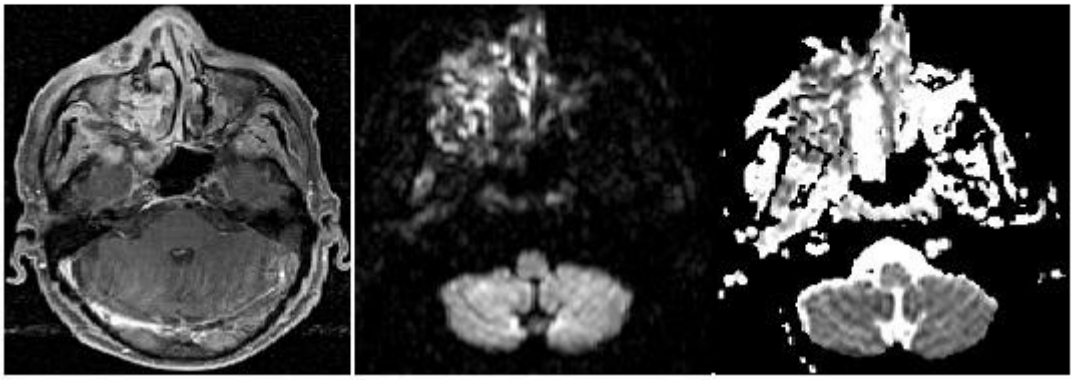

Figure 3C:

Figure3. In the parenchymal window(Preoperative axial CT images): There were soft tissue density in the right maxillary sinus, nasal cavity, in the region of the infraorbital and infratemporal. Also there was eroion in the bone front, rear and medial wall of the right maxillary sinus.

Following complete excision, the specimen was fixed in 10% formaldehyde and submitted for histopathological examination. The fixed specimen was embedded in paraffin, and 4-mm sections were stained with hematoxylin and eosin (HE), periodic acid-Schiff (PAS) stain, and Grocott's Methenamin Silver (GMS). The histopathological examination of the sample demonstrated the presence of non-septating fungal cells in the form of ribbons in large areas of necrosis, which was consistent with mucormycosis (Figure 4). There were no complications due to surgery and

antifungal therapy with 1 x 500 mg/d liposomal amphotericin B was begun promptly. Treatment was continued for 3 months in hospital. Posaconazole 3x200mg/d therapy was started when patient was discharged from hospital and used one year. After surgery, the patient was followed up with both otolaryngology and the infectious diseases clinic. Additionally, the underlying diseases (kidney disease and diabetes) were already being pursued by the clinical nephrology and endocrine clinics.

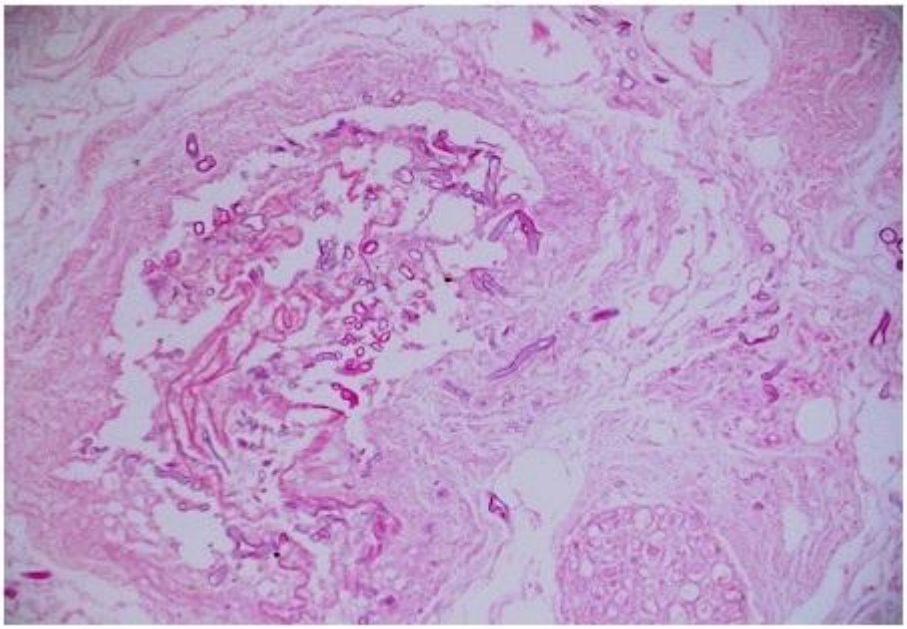

Figure4.A. The histopathological examination of the sample demonstrated in view of the deep tissues of the nasal mucosa infiltrating fungal hyphae consistent with mucormycosis (Periodic acid-Schiff (PAS) staining, H&E, 40X).B. The histopathological examination of the sample demonstrated the presence of non-septating fungal cells in the form of ribbons in large areas of necrosis (Grocott's methenamine silver (GMS) staining, 40X).

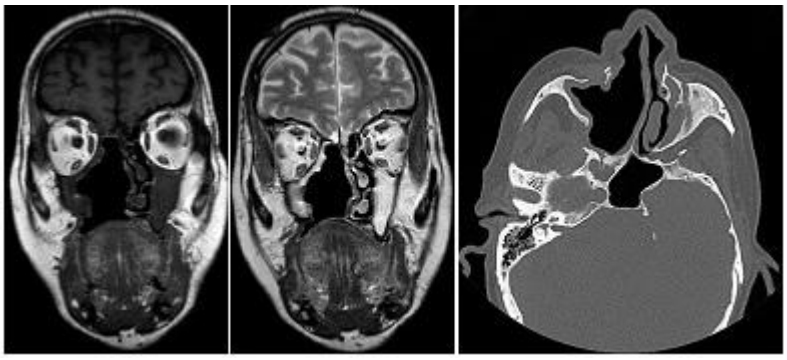

Figure 5. A. Post-op koronal T1-T2A MR ve aksiyel BT imajları: The most of right medial concha and maxillary bone was excision. There was limited to infection with surgery and antibiotic therapy. There wasnt any involvement in the infraorbital ve infratemporal areas.

B. Pre-op: unenhanced and contrast-enhanced MR images of coronal: There were intensity at the level of right maxillary sinus, nasal cavity and inferior turbinates. Also non-enhancing areas are significant for necrosis. C. Pre-op: Axial contrast-enhanced T1-weighted image in the background and diffusion-weighted images. There were increasing diffusion areas according to necrosis.

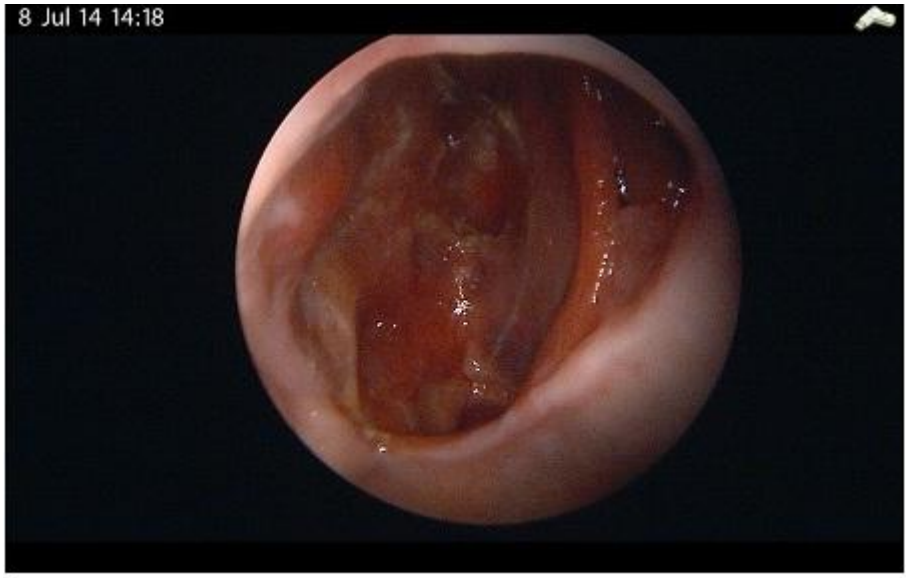

Figure 6A

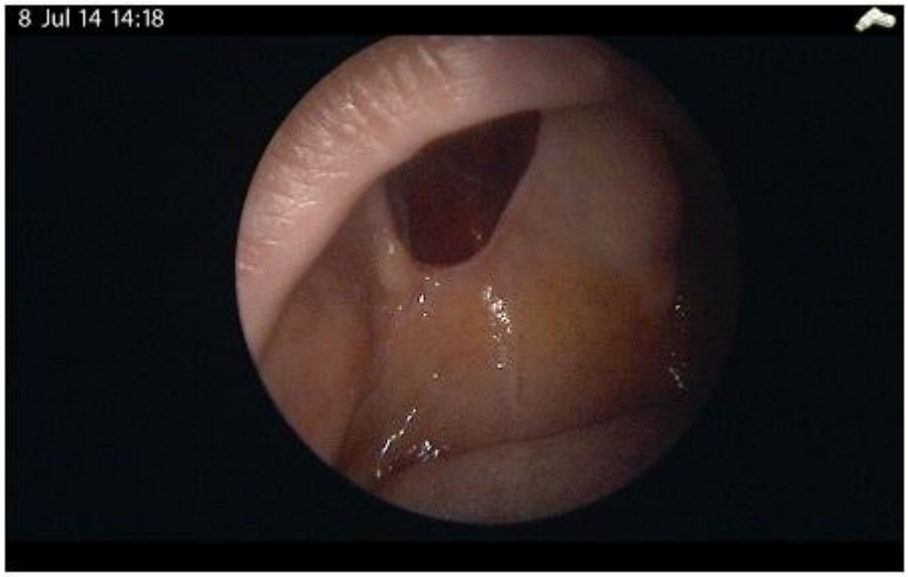

Figure 6B

Figure 6.A-B. Postoperative endoscopic view from mouth for natural mucosal of nasal and oral appearance. Also there was defect in the palate.C. Postoperative appearance of the nasal mucasa with septal perforation from view of nasal endoscopic sight.

Discussion

In Mucor was first described by Paltauf in 1885 [5], and these fungi are ubiquitous saprophytes found throughout nature. They exhibit broad (5–50 um), non-septated hyphae with right-angle branching, which characteristically involve the blood vessels, causing thrombosis and ischemia [5]. Immunocompromising conditions such as diabetes mellitus and renal disease failure are the main risk factors for mucormycosis. Mucormycosis has also been observed in patients that are receiving chemotherapy and in bone marrow transplant recipients, mostly in the developed countries. Currently, mycology, serology, histopathology, and radiology, together with technical

developments, have been increasing our chances of finding this disease in the nose and sinuses. All of these techniques are important in the resistance of a patient's response to treatment in complicated sinonasal diseases with metabolic or immunocompromising conditions suspected of having invasive fungal rhinosinusitis like mucormycosis.

Mucormycosis is observed less frequently than Aspergillus infections. However, there has been an increase in reported cases of mucormycosis in recent years [9]. The European Confederation of Medical Mycology Zygomycetes study group (ECCM) investigated 230 probable or confirmed mucormycosis cases between 2005 and 2007 in 13 European countries. They reported that 44% of these cases occurred with hematologic malignancies, 15% in trauma patients, 9% in diabetes mellitus (DM) patients, and 9% in bone marrow transplant recipients. The most common clinical involvement was pulmonary involvement, followed by rhinocerebral involvement [10]. Roden et al. [11] published a clinical study revealing 929 mucormycosis cases from 1885 to date which were investigated, and the most common sites of involvement were the sinuses (39%), lungs (24%), and skin (19%), respectively.

The most important differential feature of mucormycosis could be fatality, despite treatment. Sinus involvement was present in 66% of diabetes mellitus patients, and the mortality rate was 46% in patients with sinus mucormycosis, 76% in pulmonary mucormycosis cases, and 100% in disseminated mucormycosis cases [11]. For example, twenty-six rhinosinusitis cases due to invasive fungal infections were investigated in a study by Kasapoglu et al. [12] in our country. Additionally, invasive fungal infections due to mucormycosis were detected in seventeen of 26 patients, of whom eighteen were hematologic malignancy patients and four were diabetes mellitus patients. Eight cases resulted in death. Arda et al. [13] reported that the mortality rate of mucormycosis was 50% in their study, and diabetes mellitus (DM) was identified in three of their patients. Our patient had a history of DM for twenty years. Our patient was both diabetic and kidney disease.

Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation of mucormycosis. Mucoraceae are molds in the environment that become hyphal in body tissues. Once the spores begin to grow, fungal hyphae invade blood defenses against these fungi; thus, individuals with neutropenia or neutrophil dysfunction (diabetes, steroid use) are at the highest risk [14], like our patient.

Mucor of the sinuses may manifest as a unilateral, retro-orbital headache, facial pain, numbness, fever, hyposmia, and nasal stuffiness, which progresses to black discharge. Initially, mucormycosis may mimic sinusitis [15, 16]; however, later symptoms that indicate invasion of the orbital nerves and vessels include diplopia and visual loss, as in our patient. These late symptoms indicate a poor prognosis and are usually followed by reduced consciousness.

There are four important factors for the treatment of mucormycosis: rapid diagnosis, correction of the underlying predisposing factors, appropriate and early surgical debridement, and appropriate antifungal therapy. Mucormycosis causes significant morbidity in patients who survive, because treatment usually requires extensive, and often disfiguring, facial surgery. Before the advent of amphotericin-B, mortality rates were as high as 90 percent. However, they have been reduced to 15 to 50 percent with the combined use of surgery and amphotericin-B. Surviving mucormycosis requires rapid diagnosis, as well as aggressive coordinated medical and surgical therapy [10].

The correction of the underlying abnormality, prompt institution of liposomal amphotericin-B therapy, and surgical resection are critical [4, 14, 17]. Successful mucormycosis treatment requires the resolution of the underlying risk factor(s), antifungal therapy, and aggressive surgery.

Additionally, regular multidisciplinary follow-ups and liposomal amphotericin-B therapy are key for the success of a patient. In this case, we performed surgery and followed up with six months of liposomal amphotericin B; therefore, our patient has thus far survived. We believe that this approach is important for sino-orbital mucormycosis (see Figures 5) and there was normal appearance mucosa of palate and nasal in the endoscopic examination after surgery(Figure 6A,B,C).

No prospective comparative studies of the primary treatment of mucormycosis have been performed, largely because of the rarity of this disease. In current practice, amphotericin is the sole antifungal agent licensed by the US Food and Drug Administration for the primary therapy of mucormycosis. Antifungal treatment options consist of lipid formulations of amphotericin-B, amphotericin-B deoxycholate, or posaconazole. The first-line treatment is with an amphotericin derivative, preferably with liposomal amphotericin. Although some reports have described a combination of antifungal agents, trials are needed to determine the efficacy of this approach [18].We were used liposomal amphotericin-B for three months and posaconazole for one year to prophylaxis. There were different used of drugs in the literaures[19-20]. For example Vazgues et al [20] were used caspofungin for thirteen monts. Also Kazak et al [19] were used caspofungin for three months too. We used posaconazole used near one year and we were not encountered any complication. Currently this result our's anecdotal clinical experience in the medical therapy of sinonasal mucormycosis. Finally, more performance is necessary to prove the effectiveness of anti antifungal agents, which contains liposomal amphotericin-B, caspofungin and others. Also the early debridement of necrotic tissue in combination with medical therapy and regular follow-up are mandatory for patient survival.

Conclusion

In summary: this case report focused, in particular, on the medical therapy and follow-up after surgery in a case of mucormycosis of the sinus, which has largely been neglected in the literature. Although this is a single case study, the aim of this paper is to draw attention to the fact that antifungal therapy with regular follow-ups after surgery could present a good chance of reducing patient mortality.

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