Treatment of Extensive Maxilla, Zygoma and Orbital Wall Osteonecrosis Caused by Rhino-Orbital Mucormycosis—A Case Report

Hsin-Yi Chou, Tung-Yiu Wong, Jehn-Shyun Huang, Kuo-Ming Kuo, Ken-Chung Chen

Department of Oral and Maxillofacial Surgery, National Cheng Kung University Hospital, Tainan, Taiwan, R.O.C.

Abstract

Mucormycosis is caused by zygomycetes. This fungus can cause a variety of infections in human beings, particularly in the immunocompromised patients. Zygomycetes impinge into the vascular network, resulting in thrombosis and necrosis of the surrounding tissues. Acute necrosis of maxilla is not frequently seen, and extensive facial bone involvement is rare in patients with oral mucormycosis. Sinus mucormycosis is often accompanied by a poor prognosis and a high mortality rate (46%). Therefore aggressive surgical intervention with antifungal therapy is usually necessary.

In this report, we presented a case of rhino-orbital mucormycosis in a 60-year-old man with diabetes mellitus. Besides antifungal treatment, this patient also received several surgeries to remove all necrotic tissues, including the palate, maxilla, zygoma and orbital floor and lateral wall. Pre-bent titanium mesh on a 3D prototyping model and a temporalis muscle flap were used to do reconstruction and the results have been uneventful so far.

Key words: mucormycosis, osteonecrosis, 3D prototyping model, temporalis muscle flap.

Introduction

The first case of human mucormycosis infection was reported by Paltauf in 1885. It was caused by zygomycetes, which is a class of fungi that can cause a variety of infections in humans, particularly in the immunocompromised patients such as those with diabetes mellitus. During the past decade, mucormycosis (also called zygomycosis) became an increasingly important pathogen because of the advent of hematopoietic stem cell transplant recipients and patients with hematological malignancies. Zygomycetes are angioinvasive. The infected tissues become necrosis because of invasion of the vasculature by the hyphae. The patterns...
of infection can be divided into rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, renal zygomycosis, isolated CNS involvement or disseminated disease. The predisposing factors are patients with immuno-incompetency, diabetes mellitus, hematopoietic stem cell transplantation, hematological malignancies or long term steroid use. According to the review study, the mortality rate ranges from 10% to 100% depending on the place of infection and the underlying diseases. In sinus mucormycosis, the mortality rate is 46%. Successful treatment of mucormycosis requires early diagnosis, reversal of underlying predisposing risk factors, surgical debridement, and prompt antifungal therapy.

Usually, acute necrosis of maxilla is not frequently seen due to its rich blood vascularity, and extensive maxillary osteonecrosis is rare in patients with oral mucormyosi.

Herein, we present a 60-year-old man who had rhino-orbital mucormycosis with an underlying disease of diabetes mellitus. Besides antifungal treatment, surgical debridement to remove necrotic tissues and reconstruction was done with titanium mesh and a temporalis muscle flap.

Case presentation

This 60-year-old man had type II diabetes mellitus and received regular oral hyperglycemic agent. He received a left tonsillectomy at another hospital on Sep. 11, 2008. After the procedure, left mid-face swelling with tenderness was noted, and he was admitted for antibiotic treatment. The condition became worse, and diplopia, left facial numbness, and facial nerve weakness were noted. Paranasal sinusitis was suspected after checking computer tomography (CT), and he was transferred to our ear-nose-throat (ENT) department for further treatment.

He came to our ENT department in Oct. 2008. Admission was soon arranged under the diagnosis of acute paranasal sinusitis with left facial cellulitis. Bilateral functional endoscopic sinus surgery (FESS) was done and necrotic tissue was noted during the operation. The pathological report revealed mucormycosis. Amphotericin B was prescribed, but the patient could not tolerate the nephrotoxicity and acute renal failure occurred. His medication was shifted to posaconazole (40 mg/ml), which was formulated in oral suspension, 10 mL twice daily. The patient’s left upper second premolar exfoliated spontaneously due to bone necrosis and the dentist was consulted. Debridement via a total of four times of FESS was performed, and he was discharged after infection improvement on Nov. 24, 2008. He kept using the antifungal agent.

After one week, he came to our dental department because of multiple tooth mobility and persisted left facial swelling again was noted. We found that he had swelling and numbness over his left mid-face, left facial nerve weakness, and diplopia. Intra-oral examination presented general periodontitis, sinus tract with pus discharge at left upper central incisor edentulous ridge, gum boil at right upper first premolar buccal gingival, palate swelling, and bone exposure with oronasal communication (ONC) at the socket of his left upper second premolar (Fig. 1). Our tentative diagnosis was rhino-orbital mucormycosis, general periodontitis, osteomyelitis at the left upper premolar area with purulent oronasal communication and with suspicious palatal tumor. Incisional biopsy, incision and drainage were done at the palatal area, and he admitted for further

The pathological report on the palatal lesion was osteomyelitis and the culture grew Pseudomonas aeruginosa on Dec. 30, 2008. Ceftazidime was chosen according to the antibiotic sensitivity test, and antifungal therapy was continued using posaconazole. Insulin was prescribed instead of the oral hyperglycemic agent for its better efficiency. Magnetic resonance imaging (MRI) revealed increased infiltration, soft tissue swelling over the left periorbital and molar region, enlargement of the left lateral and inferior rectus muscles with mild exophthalmos. The suspected area of necrotic bone included the hard palate from the right first premolar to the left tuberosity, left zygomatic arch, left infraorbital wall, lateral wall and left piriform (Fig. 2). The first surgery was arranged for sequestrectomy via intra-oral approach on Jan. 2, 2008. The initial sequestrectomy removed the palate, maxilla, left maxillary sinus membrane and part of the zygoma, but preserved part of the orbital area and zygomatic arch for eyeball support (Fig. 3). The wound was packed with Iodoform gauze. This time, the pathologist noted obvious hyphae invasion into the necrotic tissue, and mucormycosis infection was confirmed again (Fig. 4). The antibiotics were shifted to Imipenem for covering Enterobacter cloacae and Pseudomonas aeruginosa with multiple-drug resistance.

The second surgery was performed on Jan. 15, 2009 for further sequestrectomy at the left zygoma, part of the zygomatic arch, pterygoid plate and part of the infraorbital wall via Weber-Fergusson incision, preserving part of the infraorbital wall to retain the position of left eyeball. The infection seemed to improve after the second debridement. Since the patient’s general condition stabilized, final debridement with reconstruction was considered.

Before the operation, a 3D model of the left orbit, zygoma and maxilla was fabricated using the computer tomography taken on Feb. 2, 2009 (Fig. 5). The titanium mesh was bent on this model to reconstruct the bony defect over the left orbital floor and lateral wall. A temporalis muscles flap (TMF) was planned to fill the defect of the maxilla. Another model of the temporalis muscle was fabricated to restore the donor site defect using the indirect method. The surgery was performed on Feb. 24, 2009, and the residual sequestra at the left zygomatic arch, piriform rim, orbital floor and lateral wall were all removed (Fig. 6). The titanium mesh was properly placed as a substitute of orbit for the left eyeball. The coronal flap was reflected and the left TMF were harvested, and it was sutured to the titanium mesh and the upper gingival. The pathological report was chronic osteomyelitis with fungal infection and consistent with mucormycosis. The final diagnosis was extensive maxilla, zygoma and orbital wall osteonecrosis caused by rhino-orbital mucormycosis.

The patient complained of oronasal communication about twenty days later, and a dehiscence was noted at the posterior margin of the muscle flap. The laboratory data was within normal limitation. No turbid fluid discharged from the dehiscence. Clinical infection symptoms and signs were not identified. The antibiotic was discontinuous on Mar. 20, 2009. He was discharged on Mar. 24, 2009, and anti-fungal therapy (posaconazole) was continued. The total hospital stay was 92 days.

During the follow-up period, oronasal
Fig. 1. Unhealed wound of left upper premolar sockets with necrotic bone exposure.

Fig. 2. MRI of sinuses with and without contrast medium.
Fig. 3. A: Necrotic maxilla was noted after flap reflection during the first surgery. B: Removal of the hard palate. C: Removal of left maxillary sinus membrane.

Fig. 4. Hyphae in soft tissue, silver stain 40x.
Fig. 5. A: 3D model for the skeletons of left orbital and temporal area (lateral view). B: 3D model of temporalis muscle covers on the temporal area (lateral view). C: 3D model of temporalis muscle covers on the temporal area (frontal view).

Fig. 6. The red line means the area of bone necrosis and was removed in our surgical treatment.
Fig. 7. A: Pre-bent titanium mesh was placed as the orbital wall. B: Harvested the temporalis muscle flap and inverted it into the mid-face to restore the soft tissue volume (arrow). C: The bone cement fabricated as the temporalis muscle was placed in the space of the donor side.

Fig. 8. CT images of sinus and orbital area. A, B: acceptable contour of titanium mesh for orbital wall. C, D: temporalis muscle flap (arrow) in left mid face.
communication still existed. Operation for repairing the defect by using palatal flap was arranged on July 2, 2009, and the dehiscence was primarily closed. The wound healed well and the patient kept taking posaconazole for a total of one year to full course and kept following up at our OPD and infection department. The recent computer tomography showed no sign recurrence with acceptable contour of titanium mesh (Fig. 8). Until now, no recurrent infection signs or symptoms have been noted clinically.

Although in this case, no immediate treatment was given, there was a little delay, and the patient could not tolerate the first choice of amphotericin B, he still successfully survived after our aggressive surgery, antibiotics and another antifungal medication, posaconazole. In order to re-establish the facial anatomy, function and esthetics, reconstruction while the patient’s condition is becoming stable is necessary, especially for those who receive aggressive surgery and a wide range of excision.

**Discussion**

Mucormycosis is caused by zygomycetes that are ubiquitous in nature, which can be found on decaying vegetation and in the soil. The first case of human mucormycosis infection was reported by Paltauf in 1885, who called it mycosis mucorina. It is the third most frequent invasive mycosis after candidiasis and aspergillosis. All humans are exposed to these fungi in our daily activities, and the fact that mucormycosis is a rare human infection reflects the effectiveness of our intact human immune system. However, mucormycosis can cause a variety of infections in humans, particularly in immunocompromised patients and those with diabetes mellitus. A review of 929 cases of zygomycosis noted that diabetes was the most common risk factor, found in 36% of cases, followed by hematologic malignancies (17%), solid organ transplantation (7%), Deferoxamine therapy (6%), injection drug use (5%), bone marrow transplantation (5%), renal failure (5%), low birth weight infant (3%), diarrhea and malnutrition (3%), HIV infection (2%), systemic lupus erythematosus (1%), and other (5%). The majority of patients with malignancy had pulmonary disease (60%), whereas the majority of patients with diabetes had sinus disease (66%). Rhinocerebral disease was seen more frequently in patients with diabetes, compared with patients with malignancy.

In mycology, the hyphae of zygomycetes are distinct and allow for a presumptive identification from clinical specimens. The hyphae are wide (10–30 μm in diameter), irregularly branched, and have no or rare septations. This is in contrast to the hyphae of ascomycetous molds, such as Aspergillus, which are narrower (2 to 5 μm in diameter), exhibit regular branching, and have many septations. Thus, it is more reliable to establish a diagnosis of mucormycosis based on a biopsy specimen of the involved tissue than by swabs or discharge. Finely mincing tissues is preferred for culturing tissue samples that may contain molds.

The maxilla rarely undergoes necrosis due to its rich vascularity. However, necrosis can occur due to bacterial infections such as osteomyelitis, viral infections such as herpes zoster, or fungal infections such as mucormycosis, etc. Several signs point towards mucormycosis. One characteristic is invasion into the vascular network, which results in thrombosis and death of surrounding tissue by loss of blood supply. There are several sites that may be affected by mucormycosis, resulting in rhino-orbital-cerebral
infection, pulmonary zygomycosis, gastrointestinal zygomycosis, cutaneous zygomycosis, renal zygomycosis, isolated CNS involvement and disseminated disease. The most common clinical presentation of mucormycosis is rhino-orbital-cerebral infection, which is presumed to start with the inhalation of spores into the paranasal sinuses. The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain. All of the sinuses become involved and the infection spreads to contiguous structures, such as the palate, orbit and brain, and usually progresses rapidly. However, there have been some reports of chronic rhino-orbital-cerebral infection with an indolent course. The most common presenting features are ophthalmologic, including ptosis, proptosis, visual loss, and ophthalmoplegia. The incidence of internal carotid artery and cavernous sinus thrombosis is higher in chronic patients than in those with the acute disease. A review of 208 cases of rhino-orbital-cerebral zygomycosis found the following frequency of signs and symptoms: fever (44%), nasal ulceration or necrosis (38%), periorbital or facial swelling (34%), decreased vision (30%), ophthalmoplegia (29%), sinusitis (26%) and headache (25%). Our patient had sinusitis with necrosis, diplopia, facial palsy, numbness and facial swelling, which was comparable with these clinical findings.

Endoscopic evaluation of the sinuses may be performed to look for tissue necrosis and to obtain specimens before open surgery. Further imaging evaluation is necessary to detect the involvement of surrounding tissue. For patients with rhino-orbital-cerebral disease, computed tomography (CT) usually reveals sinusitis only, unless bone destruction appears. Magnetic resonance imaging (MRI) is more sensitive than CT for detecting orbital and central nervous system involvement.

The successful treatment of mucormycosis requires 4 steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors if possible; (3) surgical debridement where applicable; and (4) prompt antifungal therapy. Initiation of antifungal therapy within 5 days after diagnosis is associated with improvement in survival (83% vs. 49% survival). Intravenous amphotericin B is the drug of choice. Most clinicians use a lipid formulation of amphotericin B in order to deliver a high dose with less nephrotoxicity. The usual starting dose is 5 mg/kg daily, and the dosage sometimes will increase up to as high as 10 mg/kg daily in an attempt to control the infection. In one study, amphotericin B lipid complex resulted in a 71% success rate as the salvage therapy for mucormycosis. Posaconazole, a broad-spectrum oral azole agent, is used as a step down therapy for patients who have responded to amphotericin B. The clinical efficacy of posaconazole was shown in a salvage study that enrolled 91 patients who had failed or could not tolerate the standard therapy. The rate of success (either complete or partial response) at 12 weeks after treatment initiation was 60%, and 21% of patients had stable disease. The immunosuppressed subjects who were treated for 11 weeks with combined posaconazole and lipid formulations of amphotericin B had an overall response rate similar to that of patients who were treated with posaconazole as a monotherapy. Antifungal therapy should continue until all signs of infection have been resolved, and often extends for months. In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) there
is resolution of clinical signs and symptoms of infection, (2) there is resolution or stabilization of residual radiographic signs of disease on serial imaging, and (3) there is resolution of underlying immunosuppression. In our case, intravenous amphotericin B was used as the first line of antifungal therapy, but it was stopped because of the occurrence of acute renal failure. Thus posaconazole was prescribed instead. After one year, there were no signs or symptoms of clinical infection, and the CT image revealed a stable image. The total course of posaconazole was one year.

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. The patients who do not undergo surgical debridement have a far higher mortality rate than those who undergo surgery. Combination of surgical management may have a favorable outcome.

In most cases, the prognosis for mucormycosis is poor. The mortality rate varies depending on its form and severity. According to the review study, the mortality rate is 10% (localized cutaneous type) to 100% (generalized disseminated type) depending on the infected place and underlying diseases, and it is 46% in sinus mucormycosis. Rhinocerebral mucormycosis has a higher survival rate because it frequently can be diagnosed earlier and the most common underlying cause, diabetic ketoacidosis, can be treated readily. Recent series have described a mortality rate of approximately 40% in diabetics with rhinocerebral mucormycosis. The nature of the underlying disease and the reversibility of the immune dysfunction are also important determinants of survival. One study showed that 75% of patients with rhinocerebral disease who had no underlying immunocompromised condition survived, while 60% of those with diabetes and only 20% of patients with other immunocompromised states were cured.

The face is important to human appearance and function. The infected area in our case involved the oral mucosa, sinus membrane, vessels, bony structure, and nerves. The patient may survive after active treatment, but facial deformity after removal of extensive necrotic tissues can cause a large problem for the structure integrity, esthetics and function. These also influence the patients’ mood, confidence and social ability. Reconstruction is necessary after infection has been control. Bone grafting is not suggested at the first instance for concern of refractory infection, and there might be confusion in identifying whether it is a graft failure or a recurred infection during the follow-up period. We used a titanium mesh pre-bent on a 3D prototyping model and a temporalis muscle flap to restore soft tissue volume. Although there were still some seams, there was no obvious facial concavity and the appearance is acceptable to the patient and his family.

**Conclusion**

Mucormycosis is a life-threatening infection. A diagnosis should be established as soon as possible, and the treatment plan should focus on correcting the general status, with appropriate medical treatment and aggressive surgical debridement. Investing in antifungal agents and surgery may represent the best options in increasing survival rates for patients. 3D prototyping models with pre-bent titanium
mesh help us contour the patients’ profiles more precisely, and ease the complications after operations. If the condition is stable after long term follow-up, bone grafting can also be arranged for further reconstruction.

References


治療因鼻眼窩白黴菌病所引起之上顎、顴骨及眼窩壁之骨壞死─病例報告

周欣順 王東亮 黃振勳 宋國銘 陳仲

國立成功大學醫學院附設醫院口腔醫學部口腔顱面外科

摘 要

白黴菌病是由一種存在於日常環境中的接合菌所引起，會造成多種不同部位的人體感染，尤其是免疫低下的患者。接合菌常藉由侵入血管系統，造成血栓堵塞血管、影響血液供應，進而使周圍組織壞死。在口腔白黴菌病的患者中，較少見急性的上顎骨壞死與大範圍的顱面骨壞死。一般來說，感染白黴菌病的患者預後普遍不佳。而在鼻竇感染的患者，有高達46%的致死率。治療白黴菌病，需要積極的手術介入與抗黴菌藥的合併使用。本文報告一患有糖尿病的六十歲男性，感染鼻眼窩白黴菌病，並引起大範圍之顱面骨壞死。除了抗黴菌療程外，另接受數次手術來移除位於顱部、鼻竇、顴骨、眼眶底與側壁的壞死組織。並於感染控制後，搭配事先利用三維立體模型所塑型之鈦合金網，以及顱肌皮瓣進行重建。追蹤至今並無復發。

關鍵詞：白黴菌病，骨壞死，三維模型，顱肌翻瓣。