Sultan Qaboos University Medical Journal
December 2006 Vol 6, No. 2
Sultan Qaboos University©

CASE STUDY

Mucormycosis of the Jaw after Dental Extractions: Two Case Reports

*Abdulaziz A Bakathir

تقرير عن حالتين - داء الفطرية المخاطيه في عظم الفكين بعد خلع الاسنان

الملخص: يعتبر داء الفطرية المخاطية من الالتهابات الفطرية الانتهازية نادرة الحدوث . والتي يصاب بها عادة المرضى المصابين في جهاز المناعة مثل مرضى داء السكري غير المسيطر عليه وسرطان الدم. في هذا التقرير نناقش حالتين من داء الفطرية المخاطية تم تشخيصها في عظم الفكين بعد خلع الاسنان . الحالة الاولى لشاب عمره 14 سنة مصاب بسرطان الدم الحاد النقياني وعولج بالعلاج الكيمياوي . أما الحالة الثانية فهو رجل عمره 49 سنة . اكتشف حديثا انه مصاب بداء السكر (النوع الثاني) . بعد أن ظهرت عليه علامات الحُماضٌ الكيتونيّ . وتبين أنه مصاب ايضا بسرطان الدم الأَروِمِيَّ اللِمُفاوِيّ الحاد . كانت النتيجة جيدة في كلا الحالتين بعد اجراء العلاج الجراحي والدوائي الشامل.

المفردات المفتاحية: الفطريات المخاطية . الفطريات المخاطية الانفية الدماغية . اختلاطات خلع الاسنان . تقرير حالة . عمان .

Abstract. Mucormycosis is a rare opportunistic fungal infection, which is mainly reported to occur in patients with immunocompromised conditions such as uncontrolled diabetes mellitus and leukaemias. In this paper, two cases of mucormycosis are reported after dental extractions. The first case of mucormycosis occurred in the maxilla and mandible of a 14 year old male patient undergoing chemotherapy for acute myeloid leukaemia. The second case occurred in the mandible of a 49 year old male patient with a recently diagnosed type-2 diabetes mellitus, presenting with ketoacidosis and underlying undiagnosed acute lymphoblastic leukaemia. The outcome of these reported cases of mucormycosis was favourable after comprehensive surgical and medical management.

Keywords: Mucormycosis, rhinocerebral mucormycosis, complication of dental extraction, case report, Oman

Mucormycosis (Phycomycosis, Zygomycosis) is a rare invasive opportunistic infection caused by fungi of the order mucorales. The incidence of mucormycosis is very low.[1-3] Mucormycosis mainly attacks immunocompromised patients with a rapid fulminant course.[1] The most commonly reported form of the disease is rhinocerebral mucormycosis, which is characterised by progressive fungal invasion of the hard palate, paranasal sinuses, orbit, and brain.[2-4] Successful management of this fulminant infection requires early recognition of the disease, aggressive medical and surgical interventions to prevent the high morbidity and mortality associated with the disease process.[5,6]

This paper presents two cases of mucormycosis diagnosed after dental extractions in a compromised host, which after comprehensive surgical and medical management led to favourable outcomes.

CASE REPORT 1

A 14 year old male patient with a two months diagnosis of acute myeloid leukaemia was referred to the Oral Health clinic, Sultan Qaboos University Hospital, with a chief complaint of severe toothache in the upper right premolar region, which was not controlled by simple analgesics. The patient was under chemotherapy, antiviral, antifungal and anti-biotic agents. His blood investigations clearly demonstrated pancytopenia with low

Oral Health Department, Sultan Qaboos University Hospital, Sultan Qaboos University, P.O Box 35, Al-Khod-123, Muscat, Sultanate of Oman.

**Email: abakathir@squ.edu.om*

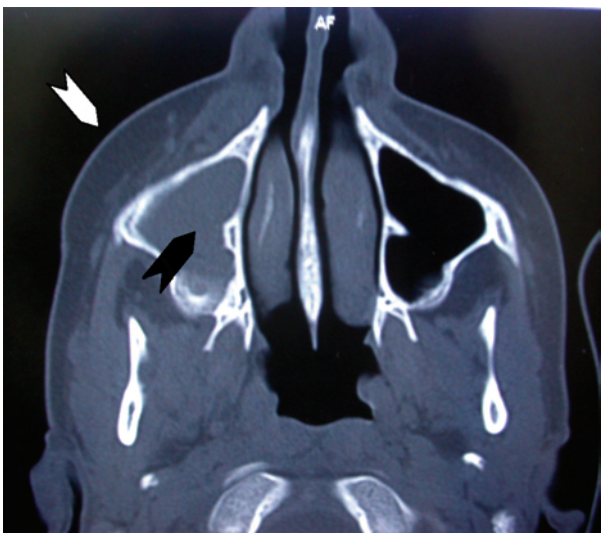

Figure 1: ***Axial CT of case 1 showing obliteration of the right maxillary sinus (black arrowhead) and soft tissue swelling over the right infra-orbital region (white arrowhead)***

platelets ($38x10^9$). Dental examination showed multiple carious teeth with a very tender and badly broken down upper right second premolar. After appropriate platelets transfusion, the upper right premolar was removed atraumatically under local anaesthesia by an Oral & Maxillofacial Surgeon. Two weeks post dental extractions, he developed a temperature of 38.1°C and complained of severe pain from the site of extraction with partial blockage of his right nostril. Clinical examination showed a febrile, fully conscious patient with Glasgow Coma scale of 15, mild right infra-orbital swelling and paraesthesia of the right infra-orbital nerve. No abnormality was observed over the right eye and nasal examination showed blockage of the right nostril with no evidence of any necrosis or nasal discharge. Intraoral examination demonstrated a tender swelling of the upper right buccal mucosa with black necrotic gingival tissue and area of necrotic bone extending from the extraction site to the adjacent teeth. In addition, the gingival necrosis had started to involve the palatal mucosal near the extraction site. Gingival and bone biopsies were taken for histopathological diagnosis. A computed tomography (CT) scan was requested and this showed a soft tissue swelling of the right infra-orbital region and marked soft tissue obliteration of the right maxillary sinus, which had started to extend medially causing obstruction of the right medial conchae and invasion of the ethmoidal air cells [Figures 1&2]. Over the next few days, the patient's condition remained much the same and the area of intraoral necrosis showed a marked increase in size. The histopathology diagnosis was positive for mucormycosis. Upon confirmation of the diagnosis of mucormycosis, the patient was started on intravenous liposomal amphotericin-B (AmBisome), after consultation with the infectious diseases team. He consented to surgical debridement under general anaesthesia and the haematology team prepared the patient for this procedure. The surgical debridement involved removal of the upper right canine, first premolar and molar, curettage of all necrotic tissues and partial maxillectomy. Ear Nose and Throat colleagues joined us to assist with the debridement using Functional Endoscopic Sinus Surgery. The area was then packed with antiseptic Bismuth Iodine Paraffin Pack (BIPP). Over the course of the next few days, the patient condition was stabilised and the sinus was continuously irrigated with 0.2% Chlorhexidine antiseptic mouth wash, 3% hydrogen peroxide solutions and the pack was regularly changed every ten days over a period of 8 weeks. The right infraorbital nerve paraesthesia had recovered well some 6 weeks post-surgical debridement. Eight weeks post-surgical curettage, the CT scan was repeated and this showed an improvement in the appearance of the right paranasal sinuses. The residual small oro-antral fistula was temporarily sealed by an obturator and its surgical repair was deferred until the patient came off chemotherapy, when all the required dental treatment was to be carried out. Unfortunately, the patient's leukaemia relapsed and more aggressive chemotherapy was planned. During the chemotherapy course, the patient complained of pain and swelling related to the carious lower right first molar and this was subsequently removed under local anaesthesia. Over the next few days the swelling and pain subsided. Ten days post extraction, a small area of necrosis started to develop buccal to the site of extraction, which continued to enlarge over the next few days with evidence of necrotic bone. Biopsy of the necrotic area was carried out and was again positive for mucormycosis. The patient was re-started on AmBisome and as the patient leukaemic status showed improvement the plan was for debridement of the site of fungal infection, followed by multiple extractions and fillings under general anaesthesia. The mucormycosis site was widely debrided, the second premolar and molar were extracted and the area was packed with BIPP. His post-operative period was uneventful, with the pack being replaced every ten days until the

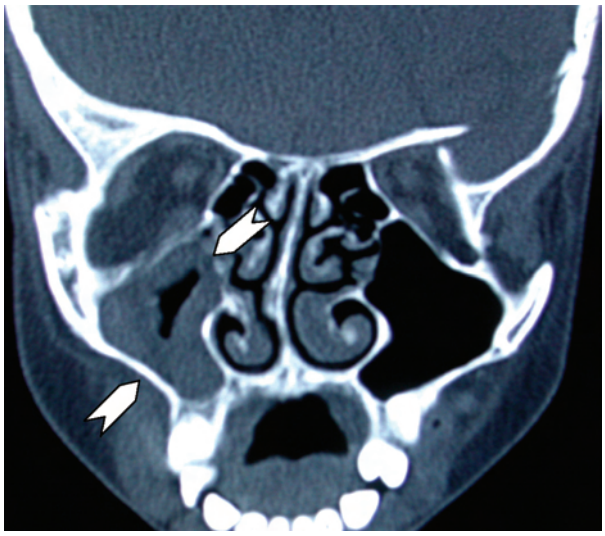

Figure 2: ***Coronal CT of case 1 showing obliteration of the right sinus causing blockage of the medial conchae and extension to the right ethmoid sinus (arrowhead)***

area had completely healed with healthy tissue, seven weeks post-surgical curettage. The patient's condition continued to improve and he underwent a successful bone marrow transplant eight months following the initial diagnosis of leukaemia.

CASE REPORT 2

A 49-year old male patient was seen in the out-patient maxillofacial clinic at the oral health department, following referral from a family medicine clinic. His chief complaint was pain at the site of a recent extraction socket and paraesthesia of the right lower lip. The patient gave a history of extraction of the lower right second molar two weeks previously at a local private clinic. His medical history revealed a recent diagnosis of type-2 diabetes mellitus (DM) and the patient was taking metformin and glipizide tablets. Clinical examination showed an afebrile, weak and pale patient with a sclera icterus. Intraoral examination demonstrated an area of soft tissue necrosis posterior to the mobile lower right first molar. A panoramic radiograph showed a non-healing socket of the lower right second molar with evidence of a small area of bone destruction and generalised horizontal bone loss indicating adult periodontitis. The patient was admitted with a provisional diagnosis of mandibular osteomyelitis and was started on intravenous augmentin and metronidazole. On admission, his complete blood count showed low haemoglobin (Hb 2.54 g/dl), marked neutropenia and pancytopenia (white cell count 1.52 $x10^9$/l, platelets 44.2 $x10^9$). His biochemical tests showed raised blood glucose (21 mmol/l), and his glycated haemoglobin was 19%. On the basis of these findings he was referred for an urgent opinion from the endocrine and the haematology teams. He was seen by an endocrinologist and the diagnosis of diabetic ketoacidosis was confirmed. The patient was started on insulin to control his diabetes. The haematology team collected a bone marrow sample, which later confirmed the diagnosis of acute lymphoblastic leukaemia and the patient was then planned for chemotherapy. The area of necrosis was debrided under local anaesthesia with appropriate platelet cover to raise the platelet count to > 50 $x10^9$. At the time of debridement, an area of black patches was seen over the bone in the right retro-molar region and a biopsy was accordingly taken for histopathology diagnosis. This was later to confirm the diagnosis of mucormycosis [Figure 3]. Following confirmation of mucormycosis, the patient was started empirically on amphotericin B (AmBisome) and further debridement of the site was planned with removal of the mobile lower right first molar and packing the area with BIPP. The debrided site was regularly packed and irrigated with antiseptic solutions (0.2% Chlorhexidine and 3% Hydrogen peroxide) every 10 days for a period of 9 weeks, until the wound healed with the formation of healthy granulation tissue.

DISCUSSION

Mucormycosis is an acute, opportunistic infection caused by a saprophytic fungus. In human beings there are three genera which are described as pathogens: *Rhizopus*, *Absibia*, and *Mucor*. These are members of the family mucorales of the class phycomycetes.[2] *Rhizopus* is the predominant micro-organism, accounting for 90% of the cases of rhinocerebral mucormycosis.[4,7] This pathogen can be found in fruits, soil, dust, and manure. In addition, it can be cultured from the oral cavity, nasal passages, throat and stools of healthy patients without a sign of disease.[8] The infectious process usually results from inhalation of spores through the nose or mouth, or sometimes through a skin laceration.[9]

Despite the fact that mucormycosis is ubiquitous and grows rapidly, it seldom causes infection in healthy patients. Therefore, if an infection with mucormycosis does occur, it usually indicates a serious underlying medical condition as reported in our two cases. Mucormycosis has been described in debilitated patients

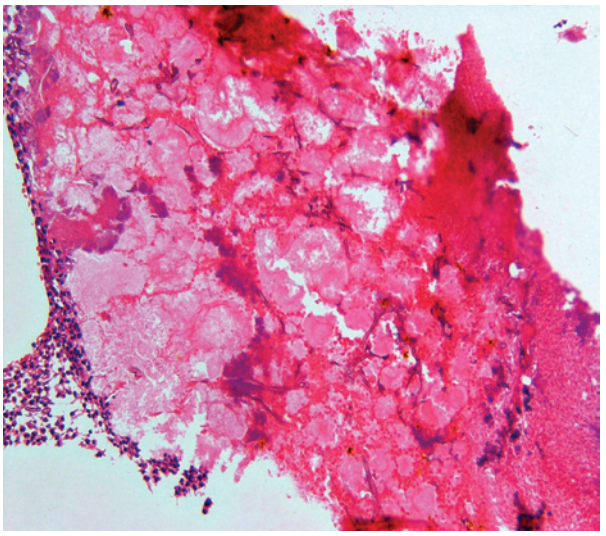

Figure 3: ***Photomicrograph from retro-molar area showing area of bone necrosis with infestation of fungal hyphae (Haematoxylin and eosin stain, original magnification _400)***

with medical conditions such as diabetes, leukaemia, lymphoma, renal failure, immunosuppressive therapy, malnutrition and severe burns.[3,8-10] Up to 40 – 50% of patients who present with mucormycosis have DM.[1,8] Studies have shown that DM alters the immunological capability to resist mucormycosis through a reduction of the phagocytic ability of granulocytes in the presence of acidosis and there is an inability of diabetic serum to inhibit *Rhizopus* in vitro.[11,12] In addition, *Rhizopus* species thrive best in an acidic and glucose-rich environment. During the state of diabetic ketoacidosis (DKA), the acidic environment and the increase in the levels of free iron ions favour fungal growth.[13] Neutrophils are also known to play an important role in the host protective response against fungal colonisation. As a result of this, patients with leukaemia have an increased susceptibility to develop fungal infections, such as mucormycosis, because of the dysfunctional neutrophils and myelosuppression resulting from chemotherapy which in turn causes a profound neutropenia.[1,13]

There are at least six clinical forms of mucormycosis: rhinocerebral, pulmonary, gastrointestinal, cutaneous, central nervous system, disseminated and miscellaneous, occurring at specific organ sites e.g. kidney and liver.[1,2,8] The term rhinocerebral mucormycosis (RM) should be used when the paranasal sinuses, orbit and brain are involved.[2-4] Amongst the paranasal sinuses, the most frequently involved are the maxillary and ethmoid sinuses.[1] RM is the most common form in patients with DKA , accounting for 70% of reported cases.[9]

Patients with rhinocerebral mucormycosis usually present with malaise, headache, facial pain, swelling and low grade fever.[8] The disease usually begins in the nasal mucosa or palate and extends to the paranasal sinuses spreading through the surrounding vessels. In addition, mucormycosis can involve the retro-orbital region by direct extension.[9,14] With orbital involvement cranial nerves III, IV and VI functions may be impaired or lost resulting in proptosis, ptosis, pupillary dilatation, orbital cellulitis and loss of vision.[8] As mucormycosis develops, the fungal hyphae start to invade local tissue. Direct penetration and growth through the wall of blood vessels account for the propensity for thrombosis and tissue necrosis as occurred in our two cases [Figure 3]. Haematogenous spread to the cavernous sinus and fatal cavernous sinus thrombosis has been widely reported.[4,8-9] Beside haematogenous spread, RM can also spread by perineural invasion.[15] An area of ulceration or an extraction socket in the mouth can be a port of entry for mucormycosis into the maxillofacial region, particularly when the patient is immunocompromised.[16] Kim et al. (2001) reported 4 cases of RM over a period of ten years, which were diagnosed post-dental extractions. In all these 4 cases, the patients had an uncontrolled DM with two of them in a DKA state at the time of presentation. Even though mucormycosis of the head and neck commonly occurs in the maxillofacial region, there are only few reported cases of RM in the mandible. [17-18] In our reported cases both patients developed mucormycosis in the mandible.

Radiographically, maxillary mucormycosis typically shows opacification of the paranasal sinuses without fluid level, thickening of the sinus mucosa and bone distraction of the sinus walls [Figures 1 & 2]. As some of these radiographic features may resemble sinusitis, McDonogh *et al.* warned that any diabetic patient in a ketoacidotic state presenting with clinical and radiographic features of rhinosinusitis should be suspected as having mucormycosis until proven otherwise.[19]

Definitive diagnosis of RM is usually obtained by a tissue biopsy which identifies the characteristic hyphae.[7] Histologically, mucormycosis is characterised by extensive tissue necrosis and the presence of numerous, large (5-30 μm), thinned-wall fungal hyphae, which are non-septate, branched at right angles and have a ribbon-like appearance [Figure 4].

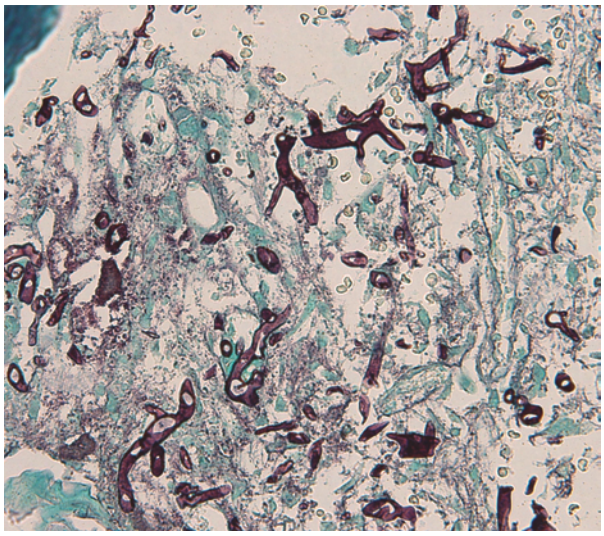

Figure 4: ***Photomicrograph from retro-molar region showing elongated, broad, non-septate branching hyphae within the tissue and the bone marrow space (Gomori methenamine silver nitrate stain, original magnification _400)***

Successful management of rhinocerebral mucormycosis includes both medical and surgical modalities. The initial medical approach to mucormycosis consists of aggressive treatment of the underlying predisposing medical condition and the use of systemic antifungal agents. The use of amphotericin B in patients with mucormycosis has been widely published and accepted as the best form of treatment with an overall survival rate of up to 72%.[7-9] Based on recent published data, Spellberg et al. highlighted the recommended use of liposomal amphotericin B such as AmBisome in the management of mucormycosis.[20] Surgical management is crucially important and should involve early debridement of all infected and necrotic tissues. This may have to be repeated based on progression of the disease. In some cases, radical resection may be required, which can include partial or total maxillectomy, mandibulectomy and orbital exenteration.[3, 21] In our reported cases, the management was started early in the course of disease and involved aggressive local debridement with repeated antiseptic packing until the wound healed with healthy granulation tissue. In addition, the correction of the underlying medical condition, along with the use of liposomal amphotericin B therapy, resulted in good control of the disease with a favourable outcome.

CONCLUSION

Early recognition of mucormycosis is necessary to limit the spread of infection, which can lead to high morbidity and mortality. Therefore, dental surgeons and medical practitioners should be familiar with signs and symptoms of the disease and should maintain a high index of suspicion in patients with DM, as it is estimated that 10% of the Omani population have diabetes. Finally, a multi-disciplinary team approach along with early diagnosis, reversal of the underlying medical condition accompanied by aggressive surgical intervention and the use of amphotericin B are the key to improving the outcome of patients with mucormycosis.

ACKNOWLEDGEMENTS

The author would like to thank Prof. K.F. Moos from Glasgow Dental Hospital, University of Glasgow, UK, for proof-reading the script and Dr. Aisha Al-Hamdani from Pathology Department at College of Medicine and Health Sciences, SQU, Oman for providing the histopathology illustrations.

REFERENCES

1. McNulty JS. Rhinocerebral Mucormycosis: Predisposing Factors. Laryngoscope 1982; 92:1140-1144.
2. deShazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Gardner L, Swain R. A new classification and diagnostic criteria for invasive fungal sinusitis. Arch Otolaryngol Head Neck Surg 1997; 123:1181-1188.
3. Tryfon S, Stanopoulos I, Kakavelas E, Nikolaidous A, Kioumis I. Rhinocerebral Mucormycosis in a Patient with latent diabetes mellitus: A Case Report. J Oral Maxillofac Surg 2002; 60:328-330.
4. Peterson KL, Wang M, Canalis RF. Rhinocerebral Mucormycosis: Evaluation of the Disease and Treatment Options. Laryngoscope 1997; 107:855-861.
5. Lehrer RI, Howard DH, Shepherd PS. Mucormycosis. Ann Intern Med 1980; 93;93-97.
6. Shand JM, Albrecht RM, Burnett III HF, Miyake A. Invasive Fungal Infection of the Midface and Orbital Complex due to Scedosporium Apiospermum and Mucormycosis. J Oral Maxillofac Surg 2004; 62:231-234.
7. Tugsel Z, Sezer B, Akalin T. Facial Swelling and Palatal Ulceration in a Diabetic Patient. Oral Surg Oral Med Oral Pathol Oral Radilo Endod 2004; 98:630-636.
8. Kim J, Fortson JK, Cook HE. A Fatal Outcome from Rhinocerebral Mucormycosis after Dental Extractions: A Case Report. J Oral Maxillofac Surg 2001; 59:693-697.

9. Sugar AM. Mucormycosis. Clin Infect Dis 1992; 14:126-129.

10. Sykes LM, Sukha A. Potential Risk of Serious Oral Infections in the Diabetes Patient: A Clinical Report. J Prosthetic Dent 2001; 86:569-573.

11. Gale GR, Welch AM. Studies of opportunistic fungi. Inhibition of Rhizopus oryzae by human serum. Am J Med Sci 1961; 241:604-608.

12. Bauer H, Flanagan JF, Sheldon WH. Experimental cerebral mucormycosis in rabbets with alloxan diabetes. Yale J Biol Med 1955; 28:29-32.

13. Damante JH, Fleury RN. Oral and rhinocerebral mucormycosis: Case Report. J Oral Maxillofac Surg 1998; 56:267-271.

14. Jones AC, Bentsen TY, Freedman PD. Mucormycosis of the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radilo Endod 1993; 75:455-460.

15. McLean FM, Ginsberg LE, Stanton CA. Perineural spread of rhinocerebral mucormycosis. Am J Neuroradiol 1996; 17:114–116.

16. Huang J-S, Kok S-H, Lee J-J, Hsu W-Y, Chiang C-P, Kuo Y-S. Extensive maxillary sequestration resulting from mucormycosis. Br J Oral Maxillofac Surg 2005; 43:532–534

17. Brown OE, Finn R. Mucormycosis of the mandible. J Oral Maxillofac Surg 1986; 44:132-135.

18. Salibsury PL, Caloss R, Cruz JM, Powell BL, Cole R, Kohut RI. Mucormycosis of the mandible after dental extraction in a patient with acute myelogenous leukaemia. Oral Surg Oral Med Oral Pathol Oral Radilo Endod 1997; 83(3):340-344.

19. McDonogh M, Human P, Odendaal W. Mucorsinisitis in diabetes. S Afr Med J 1985; 67:78-81.

20. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005; 18:556-569.

21. Ribeiro NNF, Cousin GCS, Wilson GE, Butterworth DM, Woodwards RTM. Lethal invasive mucormycosis: Case report and recommendation for treatment. Int J Oral Maxillofac Surg 2001; 30:156-159.