Worth of Time Challenge and Multi Disciplinary Team in Rhino Maxillary Mucormycosis Mortality Detraction: Longitudinal Study in Al-Salam Teaching Hospital

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Abstract

Background

Mucormycosis or Zygomycosis is a rapidly progressing fatal form of fungal infection mainly affecting the immunocompromised patients. The seriousness of such infection owing to its highly angioinvasion with high morbidity and mortality rate. At times, mucormycosis is considered as a diagnostic and therapeutic challenge to the clinicians. The multidisciplinary team (MDT) cooperation is of a substantial importance.

Objectives

For highlighting the importance of early diagnosis of Mucormycosis in immunocompromised patients; especially diabetes, we have to draw attention to the role of MDT cooperation in reducing mortality and morbidity rate. Finally emphasize the role of maxillofacial surgeon in early diagnosis and surgical treatment too.

Material and Methods

Ten cases were recorded as mucormycosis infection with diabetes mellitus for a period from 2005 to 2012 in the maxillofacial unit, Al-Salam Teaching Hospital. Patients presented with severe swelling in the maxillary posterior region within a different time in seeking treatment.

Inclusion Criteria:

- Patients diagnosed as mucormycosis.
- Patients are immunocompromised (Diabetic)

Particular dealing in management of cases after confirming attacks of mucormycosis processed including urgent amphotercine B (0.8mg/kg/day for 3 weeks) use, control the blood sugar level and surgical intervention.

Result

Although urgent treatment started, two patients died because of the late presentation (20%).

Conclusion

The key of management of this rapidly progressive fulminate disease is swift commencement of multidisciplinary treatments and early diagnosis.

Key words: Multi Disciplinary Team, Rhino Maxillary Mucormycosis, Time Challenge, Mortality Rate


Introduction

Mucormycosis or Zygomycosis is a rapidly progressing fatal form of fungal infection mainly affecting the immunocompromised patients and characterized by destruction and necrosis (1).

Mucormycosis is the most frequently used term, and it was first described by Paultauf in 1885 (2). It is an acute opportunistic infection caused by a saprophytic fungus found in soil, bread molds, and decaying fruits and vegetables. It is caused by a common inhabitant of the human upper airway (3). Rhizopus is considered the most common causative (3).
Although it is a rarity contributing to 8.3%–13.0% of all fungal infections but aggressive infection and late diagnosis make its challenges for all involved in various specialties.

The seriousness of such infection owing to a highly angioinvasive and a relentlessly progressive condition can result in high morbidity and mortality. Most of the cases are delay diagnosis too. Progression is very rapid, and dissemination to the brain may be fatal. 

Numerous predisposing risk factors are associated with mucormycosis, although most cases have been reported in poorly controlled diabetics or in patients with hematologic malignant conditions. Diabetes mellitus is the most common risk factor in the Asian continent.

Clinically the Rhino Cerebral Mucormycosis form usually presents as a parapharyngeal infection with or without an extension into the oral cavity (44%–49%).

The Rhino Cerebral Mucormycosis is further subdivided into two subtypes: a highly fatal rhino-orbito-cerebral form which is invasive and may involve the ophthalmic and internal carotid arteries and a less fatal rhino-maxillary form which involves the sphenopalatine and greater palatine arteries, resulting in thrombosis of the turbinate and necrosis of the palate.

Infections that extend from sinuses into the mouth produce painful, black necrotic ulcerations of the hard palate (the most common). Ulcers on gingiva, lip, and alveolar ridge have been reported.

The mucormycosis fungus invades the arteries, forms thrombi within the blood vessels that reduce blood supply and cause necrosis of hard and soft tissues. Once entered into the arteries, the fungus can spread to orbital and intracranial structures.

Infected tissue may appear to be normal initially and later progress to an erythematous phase with or without edema, before turning violaceous and finally forming a black necrotic eschar.

A high index of suspicion is required for an early diagnosis and initiation of adequate therapy for a good prognostic outcome. The factors influencing the pathogenicity of Mucorales are mainly:

- The availability of the iron.
- Ketoacidosis.
- pH.
- Mucorale interactions to the endothelium.

Mucormycosis of the oral cavity can be of 2 origins. One is from disseminating infection where the portal of entry is by inhalation (usually through the nose); the other is from direct wound contamination with dissemination to other viscera as a common complication. When arising from the nose and parapharyngeal sinuses, the infection may cause palatal ulceration progressing to necrosis. The area appears black in the large majority of the cases. When the infection spreads from direct wound contamination, the clinical findings may appear anywhere in the oral cavity, including the mandible.

Clinical features may range from nasal obstruction, bloody nasal discharge, facial pain or head ache, facial swelling or cellulitis, visual disturbances with concurrent proptosis in case of disseminated infections, facial paralysis in case of facial nerve involvement. As the disease progresses in to cranial vault it may lead to blindness, lethargy, seizures, and death.

At times, mucormycosis is considered as a diagnostic and therapeutic challenge to the clinicians because it presents a subtle clinical infection posing even in the setting of immunosuppression. Further, mucormycosis early diagnosis and prompt treatment becomes mandatory as it can become life threatening owing to the invasive ability of the fungi into blood vessels, embolizing to distant organs, including the brain for that urgent treatment ensuing morbidity and mortality.

Despite surgical and antifungal treatments the mortality rate is higher than 50% and even higher in immunocompromised patients.

The MDT cooperation is substantial importance as the initial medical approach to mucormycosis is to treat aggressively any underlying predisposing disorder, in the presenting cases were uncontrolled diabetes mellitus added to precise use of amphotericin B as antifungal drug of choice. Surgical management also should be initiated early in the course of treatment with MDT accordingly to level of extension (Maxillofacial, Internal Medicine Doctors, Otolaryngologist, ophthalmologist and Neurologist). All these branches share the responsibility to decrease the mortality and morbidity. Surgeries should involve debridement of all infected tissues. In some cases, radical resection may be required, which can include partial or total maxillectomy, mandibulectomy and orbital exenteration.

In dentistry, this condition gains increasing interest because of its first manifestation in the facial and oral tissue. 

The role of dentist is of immense importance because mucormycosis primarily occurs around rhinomaxillary or rhinocerebral areas involving facial tissues, palate, alveolar bone and mandibular
Mucormycosis is a fatal infection in diabetic patients with a high mortality rate. Internal Medicine Doctors, dentists should always keep in mind of this fatal infection in immune-compromised patients. An early diagnosis, combined with medical and surgical treatments, will reduce the mortality rate of this dreadful infection.

**Objectives**

For highlighting the importance of early diagnosis of Mucormycosis in immunocompromised patients; especially diabetes. We have to draw attention to the role of MDT cooperation in reducing mortality and morbidity rate. We have to emphasize the role of maxillofacial surgeon in early diagnosis and surgical treatment too.

**Material and Methods**

Maxillofacial unit in Al-Salam Teaching Hospital receives about more than fifteen immunocompromised patients monthly complain from serious odontogenic infection which needs massive urgent medical and surgical interventions.

All work is approved by the scientific committee of Nineveh Health Directory / MOH / Iraq by licenses’ Number (23161) in date (25 / 8 / 2019).

Ten cases were recorded as mucormycosis infection with diabetes mellitus for a period from 2005 to 2012. Patients presented with severe swelling in the maxillary posterior region with different time in seeking treatment.

**Inclusion Criteria:**

- Patients diagnosed as mucormycosis.
- Patients are immunocompromised (Diabetic)

**Exclusion Criteria**

- Patients diagnosed as other infections or suspected mucormycosis.
- Patients are immunocompromised (rather than Diabetic)
- Patients with poor follow up

Starting with history usually patients complain from ignored attacks of recurrent odontogenic pain, febrile and no response to antibiotics cover with rapid progressive deteriorations. All patients sustained uncontrolled diabetes mellitus added which worst the situation.

General clinical examinations underscored that patients are febrile, hypotensive, conscious and tired. Extraorally, severe swelling can be extended to the orbital region, maxillary sinus region with some degree of headache, facial and orbital pain, with opthalmologic symptoms ranging from pain, ptosis, and proptosis to opthalmoplegia and blindness. Skin red shiny in some places. Intraoral examination shows a presence of severe intraoral swelling added, extend to the maxillary tuberosity, with palatal involvement. In addition to badly broken down teeth, pus discharge in some cases. Palatal black patches are also seen in all cases with different level of extensions (A black necrotic eschar).

Radiographical examination (OPG, MRI, CT scan) show dissimilar level of bone destruction according to severity, opacification of sinuses may be observed in conjunction with patchy effacement of bony walls of sinuses.

Culture and sensitivity test with incisional biopsy are prepared for all cases to confirm diagnosis and excluding other types of infections or disease.

Clinical differential diagnosis of lesion should include squamous cell carcinoma, chronic granulomatous infection like tuberculosis, midline lethal granuloma and other deep fungal infections.

Hospitalization for each patient is mandatory trying to control the underlying disease in the internal medicine department. Neurosurgical and ophthalmological consultation also performed for patients on need according to severity and extensions.

Particular dealing in management of cases after confirming attacks of mucormycosis processed including Urgent amphotericine B (0.8mg/kg/day for 3 weeks) use; control the blood sugar level,
surgical intervention. Massive debridement for the maxillary sequestration under general anesthesia done for eight patients in different levels of extensions and approaches according to each case alone. Observation of healing process was done accurately. Patients discharge after four weeks with periodic follow up. After two months prosthetic reconstruction is well done. Unfortunately two cases died.

Records of each patient was patient identity code, demographical data, symptom onset to presentation to MaxilloFacial unit, days need to diagnose, consultation, time to start of antifungal therapy (days) from diagnosis, surgical intervention from diagnosis and lastly prognosis. Unfortunately two patients are died. Eight patients were discharged home (Table 1).

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Result

By use of SPSS version 25 statistical analyses was done. Table 1 highlights the descriptions of each patient according to time difference. Time challenge in mucormycosis is important for that we trace symptom onset to presentation in maxillofacial unit, days are need to confirm diagnosis after presentation. In all cases we consult the physicians after presentation time is needed to start of antifungal therapy days from diagnosis as well as time needed to arrange surgical treatment from diagnosis and prognosis.

Average days for presentation to the maxillofacial unit after symptom occurrence are 9.6 days (Table 2). Diagnosis for mucormycosis confirmation done by incisional biopsy at the same day of presentation and take about 7-10 days for processing the pathological section (average 7.4 days diagnosis confirmed). Although culture and sensitivity test is not dependable but it is also prepared.

Urgent consultation to the medical department done for three patients were the symptoms are highly suspicious for mucormycosis while for the others starting control of blood sugar level with intravenous antibiotic cover in the waiting period for confirming diagnosis.

On the same day of diagnosis proof, patients start the use of amphotericin B (0.8mg/kg/day for 3 weeks) with cooperation and supervision of medical specialty. Surgical debridement for the maxilla and palate arranged on the third day of diagnosis.

In spite of urgent treatment two patients died and that was caused by late presentation post (20%). (Table 1). No significant relation between days needed for presentation and days needed for diagnosis are present.

Discussion

Mucormycosis (Zygomycosis, phycomycosis) is an acute opportunistic infection caused by a saprophytic fungus that belongs to the class of phycymycetes. Different predisposing factors can prone patient to have mucormycosis infection. In this article we are focusing on diabetic cases with mucormycosis. George stated that the overall prognosis of mucormycosis remains uncertain and most progressive fatal factor were uncontrolled diabetes with prevalence 36% and mortality were 44%.

The survival rate can be improved in cases in which early detection and complete treatment are possible. In our patients the interval between diagnosis and treatment was (7.4 days), good response to treatment was observed in 8 patients while 2 patients died owing to late presentation to maxillofacial unit in spite of urgent management.

According to Yohai et al. reported a decline in the survival rate when the interval between diagnosis and treatment was longer than six days. Kohn and Helper reported a study of eight patients in whom cerebrohipphalooptalmic mucormycosis (CROM) was successfully managed without orbital exenteration; the mean temporal interval between the onset of symptoms and diagnosis in these patients was four days. Schwartz et al. analyzed 99 studies in the literature regarding different types of this disease, and their analysis revealed a grim picture of the problem.

Late presentation in two patients with aggressive infection extension to ophthalmic and brain area resulted in loss of these two cases even after urgent starting of amphotercine B giving mortality rate 20%.
Amphotericin B has improved the survival rate in diabetics to 79% versus 37% in diabetics who did not receive the drug. The overall prognosis is better in diabetic patients because they have a more rapidly controllable and reversible.

Recent reports show that the overall mortality rate following the widespread use of amphotericin B in conjunction with surgical debridement has fallen to 40%.

Individual use of amphotericin B is not enough to cure patients; surgical debridement is also mandatory according to level of extensions of necrotic eschar with mutual aid team work with other specialty as ophthalmology and neurologist.

George Petrikkos concentrated on aggressive surgical debridement of infected tissues coupled with the excision of localized lesions is necessary because vascular thrombosis prevents systemically administered drugs from reaching the infected tissues.

In our study, we adopted the principles of debridement and excision prepared until they reach healthy tissues or bone to be sure that the sequestrum is removed. Because mucormycosis is a vaso-occlusive disease, the affected tissues rarely bleed upon debridement or excision, so the surgical procedure should be continued until normal, well-perfuse bleeding tissue is observed. Drainage of the paranasal sinuses or orbital exenteration may be required.

It is essential for the clinician to maintain a high index of suspicion in populations at risk, as early diagnosis can be life-savings.

MDT cooperation is essential in the management of such cases. Each specialty advocate his role to prevent rapidly progress from isolated sinus involvement to direct orbital extension leading to ophthalmoplegia, and eventual blindness and or intracranial extension which occurs in 80% of cases and leading to cavernous sinus thrombosis and cerebrovascular accidents. Early diagnosis and subsequent treatment has been shown to portend higher survivability.

A review if 929 reported cases of mucormycosis showed survivability was only 3% in patients who were untreated, none of whom had the rhinocerebral variant of the disease. The mainstay of treatment remains aggressive surgical debridement, antifungal therapy, and reversal of underlying predisposing factors.

The key to management of this rapidly progressive fulminate disease is swift commencement of multidisciplinary treatments. These patients should be treated in tertiary care centers with the availability of maxillofacial surgeon, otolaryngology, ophthalmology, neurologist, and infectious disease specialists so as to execute efficient and expeditious treatment. We feel that the rapid initiation of an aggressive multifaceted surgical and medical treatment regimen can confer an improved overall prognosis, and propose treating mucormycosis.

Conclusion

Given the high morbidity and mortality of invasive rhino-orbito-cerebral fungal infections, a comprehensive and efficient multidisciplinary approach must be executed. This includes early and aggressive surgical debridement of disease in the paranasal sinuses, foramina of the skull base, and intracranial components, as well as initiation of a robust anti-fungal medical regimen with close follow-up. Despite aggressive measures, the overall mortality of rhinocerebral mucormycosis remains high, and future studies must focus on avenues of securing an early diagnosis, enacting aggressive multidisciplinary management, and pursuing new avenues of treatment.

Abbreviations
MDT Multidisciplinary Team
OPG Orthopantomography.
MRI Magnetic Resonance Imaging
CT Scan Computed Tomography
TT Treatment

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✓ We are honored to thank all of:
Conflict of Interest
The authors of this study declare no conflict of interest.

References
5. Hariprasath Prakash and Arunaloke Chakrabarti. Global Epidemiology of Mucormycosis. Journal of Fungi Review. Received: 11 February 2019; Accepted: 16 March 2019; Published: 21 March 2019
<table>
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<tr>
<th>Patient ID</th>
<th>Symptom Onset to Presentation in Maxillofacial Unit</th>
<th>Days to Diagnosis After Presentation</th>
<th>Consultation After Presentation</th>
<th>Time to Start of Antifungal Therapy** (Days) From Diagnosis</th>
<th>Surgical TT From Diagnosis</th>
<th>Prognosis</th>
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Table 1: Descriptive details of each patient according to time

<table>
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<tr>
<th></th>
<th>Symptom onset to presentation in MaxilloFacial Unit</th>
<th>Days to diagnosis</th>
<th>Consultation After presentation</th>
<th>Time to start of antifungal therapy** (days) From diagnosis</th>
<th>Surgical TT From diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>D9</td>
<td>D9</td>
<td>1 D after</td>
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<td>D3</td>
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Table 2: Descriptive Statistics (average)

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<tr>
<td>Days to diagnosis</td>
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<td>4.00</td>
<td>9.00</td>
<td>7.4000</td>
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<tr>
<td>Consultation After presentation</td>
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<td>.00</td>
<td>7.00</td>
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</tr>
<tr>
<td>Time to start of antifungal therapy** (days) From diagnosis</td>
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<td>.00</td>
<td>.00</td>
<td>.0000</td>
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<tr>
<td>Surgical TT From diagnosis</td>
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<td>3.00</td>
<td>3.00</td>
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Table 3: Chi-Square Tests for Cases Sample

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<tr>
<th>Correlations</th>
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<th>Consultation</th>
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<table>
<thead>
<tr>
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<tr>
<td><strong>Days to Diagnosis</strong></td>
<td>Correlation</td>
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<td>P - Value</td>
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<td></td>
<td>N</td>
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<td><strong>Consultation After Presentation</strong></td>
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**. Correlation is significant at the 0.01 level (2-tailed).  
*. Correlation is significant at the 0.05 level (2-tailed).  

<table>
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<th>Chi-Square Tests</th>
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a. 45 cells (100.0%) have expected count less than 5. The minimum expected count is .10.

Figure 1: Extensive infection (late presentation)
Figure 2: Palatial Esche

Figure 3: OPG Radiographical interpretation

Figure 4: CT scan (Radiographical view)
Figure 5: Histopathological report (incisional biopsy)

Figure 6: Post surgical palate healing

Figure 7: Obturater partial prosthesis