Rhino-Orbito-Cerebral Mucormycosis: Clinical Presentation and Outcome

Objective: To document the presentation and outcome of mucormycosis.

Materials and Methods: The study was conducted on ten cases that presented over seven years' period (May 2000 to May 2007). All cases were presented in Holy Family Hospital Rawalpindi with advanced features of mucormycosis. A proforma was allocated to every patient to record, present and past history of disease, history of allergy, upper respiratory tract infections and personal history. Patients were assessed for age, gender, predisposing factors, symptoms and signs, sites of extension, number and sites of debridement and outcome.

Results: Age range was 18 to 60 years. Predisposing factor was Diabetes mellitus in all patients, with ketoacidosis in two and renal failure in one. Dark necrotic nasal crusts in four, facial pain in seven, ocular involvement including proptosis in seven, ophthalmoplegia in five, necrosis of palate in one, CNS involvement in three and hemiplegia in two. All patients were treated with intravenous Amphotericin-B, followed by surgical debridement. Various surgical interventions were used, including ethmoidectomy, sphenoidectomy, partial or radical maxillectomy etc. Six patients died due to various causes, one lost to follow up, three were alive and disease free (1 to 5 years).

Conclusion: Rhino-orbito-cerebral mucormycosis in present case series was mostly seen in middle aged diabetics. ENT, ocular and CNS features were common. As most of the cases presented in advanced stages, the disease had high mortality. Amphotericin-B and thorough surgical debridement are the mainstay of the treatment; with control of the predisposing factors.

Key Words: Rhino-orbito-cerebral mucormycosis, presentation and outcome.

Introduction

Mucormycosis is a rare, invasive, fungal infection caused by fungi of the class phycymycetes.1 The sites of pre-dilection for this infection are the nose and paranasal sinuses from where it progresses to involve the orbit and at times intracranial structures such as the cavernous sinus and the cerebral hemispheres.2 Rhino-orbito-cerebral mucormycosis mainly occurs in immuno-compromised patients. Poorly controlled diabetics, immunosuppression with corticosteroids, hematological malignancy, solid malignancy, iron overload and burns are some of the conditions which predispose patients to the development of this disease.3 Treatment consists of control of the underlying condition predisposing the patient to the infection, aggressive surgical debridement and intravenous broad spectrum antifungal, Amphotericin B.4 Even with treatment, mortality remains high and in patients who survive the residual morbidity is extensive. It is important that this infection be recognized and adequately treated but there is a paucity of literature on this in Pakistan with available information being restricted to few case reports5,6,7 and one case series.8 The fungi are commonly found in the mucosa of the nasal and paranasal sinuses of most individuals and in the absence of predisposing factors, the body's innate defenses prevents them from developing this invasive and frequently fatal infection which usually starts from the nose and paranasal sinuses and can potentially progress in any direction. The fungi are vasoinvasive and locally destructive but their main pathogenic mechanism is growth along the blood vessels, invasion of the lumen and formation of mycotic thrombi which are said to lead to mycotic emboli.9,10

All three of the maxillary, ethmoid and sphenoid sinuses and in addition, the pterygopalatine fossa have been mentioned as the possible routes of spread to the orbit.11 Within the orbit, the fungi cause extensive
invasion on the extraocular muscles and lead to ophthalmoplegia and proptosis. In addition to involvement of orbital contents leading to these findings, they are also frequently attributed to cavernous sinus thrombosis.9,10,12

We report the presentations and outcome of rhino-orbital mucormycosis in a case series of 10 patients presenting over 7 years to Holy Family Teaching Hospital, Rawalpindi.

Materials and Methods

This case series is based on the review of case records of 10 patients presenting between May 2000 and May 2007 to the departments of Otorhinolaryngology, Ophthalmology or Internal Medicine at Holy Family Teaching Hospital, Rawalpindi, Pakistan. In all the patients, diagnosis of rhino-orbital mucormycosis was confirmed by histopathology of biopsy specimens which in all cases showed broad, nonseptate, hyphae branching at right angles, consistent with mucor. Parameters included were: age, gender, predisposing factors, symptoms and signs, sites of extension, number and sites of debridement and finally, outcome.

Results

Ten patients, four females and six males were included in this study. Age range was 18 to 60 years with a median of 48 years. Diabetes mellitus was a predisposing factor in all the patients; two of them had ketoacidosis and one renal failure. Fatigue was reported by all patients, fever in five. Dark necrotic nasal crusts were observed in four, facial pain in seven, ocular involvement including proptosis in seven, ophthalmoplegia in five, necrosis of palate in one, CNS involvement in three, and hemiplegia in two patients.

Table I: Clinical details in Patients of Rhino-Orbital-Cerebral Mucormycosis

<table>
<thead>
<tr>
<th>Case No/ Age</th>
<th>Predisp Leading Factors</th>
<th>Symptoms and Signs</th>
<th>Mucor extension</th>
<th>Medical Therapy</th>
<th>Debridement</th>
<th>No of Debridements</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/18</td>
<td>Diabetic Ketoadesis is</td>
<td>Facial pain, edema/necrosis of nasal mucosa, proptosis</td>
<td>Nose, sinuses, orbit</td>
<td>Diabetes control Amphotericin B and supportive measures</td>
<td>Subbial facial dehiscing debridement from nose and sinuses by Caldwell luc approach Ethmoidectomy/sphenoidectomy</td>
<td>2</td>
<td>Alive, disease free after 5 years</td>
</tr>
<tr>
<td>2/M/27</td>
<td>Facial pain, proptosis necrosis of palatal and nasal mucosa, ophthalmoplegia</td>
<td>Nose, sinuses, orbit pterygopalatine fossa</td>
<td>Diabetes control Amphotericin B and supportive measures</td>
<td>Subbial facial dehiscing debridement from nose and sinuses by Caldwell luc approach Ethmoidectomy/sphenoidectomy left unilateral orbital exenteration</td>
<td>3</td>
<td>Alive, disease free after 4 years</td>
<td></td>
</tr>
<tr>
<td>3/M/60 Episode of diabetic coma</td>
<td>Facial pain, proptosis ophthalmoplegia, black eschar on cheek necrosis of nasal mucosa, headache, sequees</td>
<td>Nose, sinuses, orbit, facial soft tissues brain</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Combined neurosurgical and ENT debridement of disease</td>
<td>1</td>
<td>Died due to recurrence and extensive CNS involvement</td>
<td></td>
</tr>
<tr>
<td>4/M/50 Renal failure</td>
<td>Severe headache proptosis nasal obstruction, seizures hemiplegia</td>
<td>Sinuses, brain</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Combined neurosurgical and ENT debridement of disease</td>
<td>1</td>
<td>Died due to recurrence and extensive CNS involvement</td>
<td></td>
</tr>
<tr>
<td>5/M/53 Ketoadesis is</td>
<td>Facial pain, Nasal Obstruction, ophthalmoplegia proptosis, black eschar overlying left maxilla</td>
<td>Nose, sinuses, facial soft tissue, orbit brain</td>
<td>Diabetes control Amphotericin B and supportive measures</td>
<td>Debridement from nose and sinuses by Caldwell Luc approach ethmoidectomy sphenoidectomy unilateral orbital exenteration</td>
<td>1</td>
<td>Died due to recurrence CNS involvement</td>
<td></td>
</tr>
<tr>
<td>6/M/60</td>
<td>Ophthalmoplegia proptosis, black eschar on cheek, edema, facial pain</td>
<td>Sinuses, facial soft tissue, orbit</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Debridement from nose and sinuses by Caldwell Luc approach ethmoidectomy sphenoidectomy unilateral orbital exenteration</td>
<td>1</td>
<td>Died due to recurrence and extensive CNS involvement</td>
<td></td>
</tr>
<tr>
<td>7/F/45 Diabetes mellitus</td>
<td>Ophthalmoplegia, proptosis, facial swelling, black eschar on cheek</td>
<td>Sinuses, facial soft tissue, orbit, orbit</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Debridement from nose and sinuses by Caldwell Luc approach ethmoidectomy sphenoidectomy unilateral orbital exenteration</td>
<td>1</td>
<td>Died due to recurrence and extensive CNS involvement</td>
<td></td>
</tr>
<tr>
<td>8/M/45 Diabetes mellitus</td>
<td>Severe headache, nasal obstruction, necrosis of nasal mucosa, facial pain proptosis, hemiplegia</td>
<td>Nose, sinuses, orbit brain</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Debridement form nose and sinuses by Caldwell Luc approach Ethmoidectomy sphenoidectomy unilateral orbital exenteration</td>
<td>1</td>
<td>Died due extensive CNS involvement</td>
<td></td>
</tr>
<tr>
<td>9/F/45 Diabetes mellitus</td>
<td>Proptosis, Palate, nose sinuses, brain</td>
<td>Palate, nose sinuses, brain</td>
<td>Amphotericin B General and Supportive measures</td>
<td>Nil</td>
<td></td>
<td>Lost to follow up</td>
<td></td>
</tr>
<tr>
<td>10/F/45 Diabetes mellitus</td>
<td>Headache</td>
<td>Sinuses, orbit</td>
<td>Diabetes control Amphotericin B General and Supportive measures</td>
<td>Debridement from nose and sinuses by Caldwell Luc approach Ethmoidectomy sphenoidectomy unilateral orbital exenteration</td>
<td>1</td>
<td>Alive and disease free after 1 year</td>
<td></td>
</tr>
</tbody>
</table>

CT scan of paranasal sinuses was performed which showed mucoperiosteal thickening and opacification of the ethmoid and maxillary sinuses with only bony erosion. Asymmetry of pterygopalatine fossa was noted in two patients. All patients were treated with intravenous Amphotericin B and surgical debridement.
Surgical intervention included ethmoidectomy, sphenoidectomy, partial or radical maxillectomy and debridement of the cheek soft tissue and pterygopalatine fossa with or without orbital exenteration. The most frequent approach for debridement was sublabial facial degloving.

Five patients died: one expired due to uncontrolled diabetic ketoacidosis and underlying disease; two due to recurrence and later CNS involvement and another two due to extensive CNS involvement.

Discussion

Rhino-orbito-cerebral mucormycosis is an opportunistic fungal infection caused by fungal spores which are ubiquitous in nature. The cases are commonly reported from the subcontinent and are rarely seen in Europe or the Americas.\(^1\)\(^-\)\(^3\) The infection usually starts from the nose and paranasal sinuses, where it causes nasal discharge and nasal blockade, and progressive formation of necrotic eschar on the mucosa of the nose, most frequently on the middle and inferior turbinate, as seen in 4 of our patients. In the case series of Yohai et al.,\(^14\) 48% patients had nasal ulceration and presence of necrotic nasal eschar. The infection to the orbit of the same side frequently occurs and the pathways of spread are not clearly delineated. Seven out of the ten patients in our series complained of ocular pain and proptosis while 5 showed ophthalmoplegia on examination. Besides its vascular and local invasion, the fungi are known to damage nerves as well.\(^15\) These properties probably account for the ocular symptoms of the patients but in the absence of MRI and autopsy findings, it is difficult to rule out cavernous sinus thrombosis as a cause as well. The frequency of ocular symptoms is congruent to Yohai et al.,\(^14\) who report that 64-67% patients had ocular symptoms. The fungi are known to frequently involve the central nervous system by the aforementioned vasoinvasive mechanisms as well as through direct spread.\(^15\) Involvement of any part of the brain is possible, depending upon the initial site of entry of the fungi into the cranium. In such cases, headache is common along with hemiplegia of the contralateral side, seen in perieto-temporal involvement.\(^16\) Three patients in the present case series had involvement of the central nervous system with 2 developing hemiplegia. In addition to the destruction in the brain substance, the fungi are known to directly invade and thrombose the internal carotid artery,\(^17\) another potential cause of hemiplegia; however, none of our patients underwent carotid arteriography so definite conclusions on the cause of hemiplegia in our patients can not be made.

All the 10 patients in our study had diabetes mellitus, while it is known to be the predisposing factor in 60-81% patients having rhino-orbito-cerebral mucormycosis.\(^14\) This high frequency of diabetes maybe explained by the fact that in a third world country such as Pakistan, with abysmal health care availability, many diabetics are unaware of their condition hence leading to uncontrolled hyperglycemia and ketoacidosis in some, which predisposes the patients to this devastating infection. Hence, better knowledge and availability of healthcare for people with diabetes maybe helpful in reducing the incidence of this potentially fatal disease in our settings.

The treatment of rhino-orbito-cerebral mucormycosis is based on three principles. The first is effective control of the predisposing condition. This bolsters the patient’s own immunity to fight off the infection.\(^16\)\(^,\)\(^18\) Indeed one the patients in our case series died due to uncontrolled diabetes.

The second major factor is the fungistatic drug amphotericin B. The drug administered intravenously, usually at a dose of 1mg/kg/day to a total dose of 3-3.5 gms, confers proven survival benefits in patients with mucormycosis.\(^19\) The third important intervention is surgical debridement. All but one of the patients in the present series underwent surgical debridement. In the patients who had involvement of the maxillary sinus, the pterygopalatine fossa was also explored and the surgeon, in all cases found involvement of the pterygopalatine fossa. This confirms the findings of Hosseini and Borghel that the pterygopalatine fossa is invariably involved in the spread of the infection and may actually serve as a reservoir of disease, leading to recurrence despite adequate surgical debridement.\(^13\) Hence, the authors support the recommendation that while operating on all cases of rhino-orbito-cerebral mucormycosis, an attempt should be made to explore and eradicate the disease from the pterygopalatine fossa on the affected side.

Five of the ten patients in this series died while one left against medical advice and was lost to follow up. Yohai et al, in their extensive case study and literature review, reported the survival in patients with diabetes to be 77% as compared to only 34% in nondiabetics (otherwise immuno-compromised).\(^14\) The better survival in diabetics is perhaps due to better capabilities of present therapeutic regimens to check hyperglycemia and ketoacidosis, which is very important in prognosis of diabetics with rhino-orbito-cerebral mucormycosis. According to Ferry et al,\(^20\) delay in diagnosis and treatment is a bad prognosticator in this condition, and patients in our settings usually present to a tertiary care facility such as ours, only when the disease is quite extensive. Lehrer et al,\(^21\) have also found that the patients most likely to survive are those who are diabetics and have localized mucormycosis infection in the head and neck region. This also adds strength to our hypothesis that delay in presentation was responsible for the relatively lower frequency of survival
in our patients. This also highlights the importance of studies which describe the presenting features of this disease because that can help medical practitioners, especially those in primary care settings who get to see the patients first, to better diagnose and promptly refer the patient to a tertiary care hospital for immediate institution of treatment.

Conclusion

Rhino-orbital mucormycosis was mostly seen in middle aged diabetics. ENT and ophthalmologic symptoms are common. An aggressive early treatment can limit mortality related to this disease. Pterygopalatine fossa should always be explored to eradicate the reservoir of infection.

References