Clinical features, diagnosis, and outcomes of rhino-orbito-cerebral mucormycosis-A retrospective analysis

Abdollahi A¹, Shokohi T²,³*, Amirrajab N⁴, Poormosa R⁵, Kasiri AM⁶, Motahari SJ⁷, Ghoreyshi SM⁵, Madani SA⁵, Nikkhah M⁵, Ghasemi M⁵, Vahedi Larijani L⁶, Didehdar M⁷, Seifi Z⁴, Gholinejad N¹, Ilkit M⁸

¹ Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
² Department of Medical Mycology and Parasitology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
³ Invasive Fungi Research Center (IFRC), Mazandaran University of Medical Sciences, Sari, Iran
⁴ Department of Medical Laboratory Sciences, School of Paramedicine/Infectious and Tropical Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
⁵ Department of Otolaryngology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
⁶ Department of Pathology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
⁷ Department of Medical Mycology and Parasitology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
⁸ Division of Mycology, Department of Microbiology, School of Medicine, University of Çukurova, Adana, Turkey

*Corresponding author: Tahereh Shokohi, Department of Medical Mycology and Parasitology, Invasive Fungi Research Center (IFRC), School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. Email: shokohi.tahereh@gmail.com

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Abstract

Background and Purpose: Rhino-orbito-cerebral mucormycosis (ROCM) is a rare disease with acute and fulminating manifestation. This infection is associated with high morbidity and mortality rates. Herein, we reviewed the manifestations, underlying conditions, medical treatments, and surgical interventions in ROCM patients admitted to a tertiary referral center in northern Iran over a seven-year period.

Materials and Methods: In a retrospective analysis, 15 cases of ROCM were identified from 2007 to 2013 in Bu Ali Sina Hospital, Sari, Iran. All the ROCM cases were clinically diagnosed and confirmed by histopathological and/or mycological examination. The relevant demographic data, clinical, ophthalmic, and neurologic manifestations, underlying conditions, medical treatments, and surgical interventions were recorded and analyzed.

Results: The mean age of the patients was 54±11 years (age range: 28–70 years); 26.7% of the patients were male and 73.3% female (male: female ratio of 1: 2.7). Uncontrolled diabetes was noted in at least 86.7% (13/15) of the cases. The maxillary sinuses were the most frequently involved sites (66.7% of the cases) followed by the ethmoid sinus. Amphotericin B in combination with surgical debridement was used in the treatment of 80% of the cases. Furthermore, 73.3% of the patients who were diagnosed early and underwent medical and extensive surgical debridement of the infected tissues survived.

Conclusion: Uncontrolled diabetes mellitus is considered to be the main predisposing factor for ROCM. To prevent and reduce mortality rate of this acute disease, early diagnosis based on clinical findings and biopsy is recommended.

Keywords: Diabetes, Iran, Rhino-orbito-cerebral mucormycosis, ROCM, Zygomyces

How to cite this paper:

Introduction

Rhino-orbito-cerebral mucormycosis (ROCM) is a fulminant fungal infection associated with high morbidity and mortality rates [1–3]. Diabetes is the most common predisposing factor for ROCM [4, 5]. Other predisposing factors include malignant hematological disorders, metabolic acidosis, deferroxamine and glucocorticoid therapy, and chronic renal failure [6, 7]. Opportunistic fungi, belonging to the order Mucorales, are responsible for this rapidly progressing fatal infection [8–11]. Among the several Mucorales genera, species from the genus Rhizopus are the most common causes of ROCM and are detected in the majority of cases, followed by Lichtheimia, Mucor, Rhizomucor, Saksenaea, Apophysomyces, and Cunninghamella [12, 13]. Following the inhalation of fungal spores that are present in the environment [14], the fungi colonize the nasal/sinus mucosa and cause infection in neighboring areas including the orbit, cavernous sinus, and brain [15]. The Mucoralean fungi have angio-invasive ability and cause thrombosis of blood vessel leading...
to tissue necrosis [16]. It is believed that acidosis facilitates the invasion of blood vessel walls by these fungi because these fungi have keto-reductase system, which activate in acidic pH caused by uncontrolled diabetes [17].

Although the combination of host factors, clinical manifestations, and radiological findings may help with early diagnosis of mucormycosis, definitive diagnosis relies on direct microscopy, histopathology, and culture of tissue samples. Deep tissue biopsy of the involved site is commonly cumbersome because the patients are often too unstable to undergo invasive procedures [18, 19]. Due to delicacy, fragility, and low viability of fungal elements, culture results are often negative. Although advanced molecular and other non-culture based approaches are promising and may improve and complement the conventional methods, diagnosis of mucormycosis remains a challenge [20]. Early diagnosis of sino-nasal mucormycosis, management of the underlying condition, and prompt therapeutic interventions are critical for the prevention of invasion to the orbital and cerebral tissues. In the current study, we reviewed the confirmed cases of ROCM (2007–2013) referred to Bu-Ali Sina Hospital, a university-affiliated tertiary referral hospital in northern Iran, during a period of seven years. We evaluated the patients’ demographic characteristics, underlying diseases, clinical manifestations, management, and disease outcomes.

**Materials and Methods**

**Study patients**

A retrospective study was conducted on ROCM cases (2007-2013) that were recorded at the Ear, Nose and Throat (ENT) Department of Bu-Ali Sina Hospital in Sari, Iran, during a period of seven years. The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.95.1560). As this was a retrospective analysis of medical records, no written informed consent was obtained from the patients.

**Patient definition**

According to the criteria put forth by the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for invasive fungal disease (IFD) [18], patients with mycological and histopathological evidence of mucormycosis in tissue biopsy (including observation of aseptate hyphae branching at wide angle and ribbon-like hyphae associated with tissue damage) taken by functional endoscopy sinus surgery (FESS) or needle aspiration were considered in the study as a proven case. Direct examination of biopsy or aspirated material was performed using 10% potassium hydroxide (KOH) or calcofluor white (CFW) staining solution (Polysciences, Inc., Warrington, PA, USA) [21]. The specimens were inoculated on Sabouraud dextrose agar (SDA, Difco) with antibiotics (50 µg/ml chloramphenicol) and incubated at 30°C up to one week. Rapid growth of grey fluffy colonies resembling cotton candy was identified at genus level based on the conventional morphological method. The growth of pure and similar colonies of Mucorales on more than one culture media was considered significant [21].

All the demographic and clinical characteristics comprising of ophthalmic and neurologic manifestations, underlying conditions, as well as medical and surgical interventions were recorded in specific data sheets and analyzed. Data obtained from computed tomography (CT) scanning of paranasal sinuses, such as the evidence of mucosal thickening, turbidity, fluid levels, bone destruction, and osteomyelitis, were recorded in data sheets, as well. To analyze the data, descriptive statistics were used in SPSS, version 14.

**Results**

Over the seven-year period, 15 patients diagnosed with ROCM met the inclusion criteria. The demographic characteristics, underlying conditions, clinical manifestations, medical and surgical interventions, and diagnoses were outlined in Table 1.

The mean age of the patients was 54±11 years (age range: 28–70 years); 4 out of 15 patients (26.7%) were male and 11 (73.3%) patients were female (male: female ratio of 1: 2.7). Twelve (86.7%) patients had uncontrolled diabetes and two (13.3%) had hematological disorders; among the latter, one patient (case no. 4) had acute myeloid leukemia (AML), one patient (case no. 3) T-cell lymphoma, and one patient (case no. 2) suffered from beta-thalassemia major and secondary diabetes mellitus.

The maxillary sinus was the most frequently affected sinus (10 patients; 66.7%) followed by the ethmoid sinus (8 patients; 53.3%) and sphenoid sinus (three patients; 20%). Orbital involvement was apparent in six (40%) cases. Necrosis of the hard palate was observed in patients no. 3 and 10; both patients expired. The clinical signs and symptoms of infection in ROCM cases were presented in Table 1. Ophthalmic and facial involvements were the most common evidence of ROCM. Periorbital swelling, ocular pain, ocular ptosis and proptosis, and loss of vision were observed in 13 (86.7%) patients; facial pain, swelling, and dysesthesia at the affected site were
<table>
<thead>
<tr>
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<th>Sex/age</th>
<th>Underlying disease*</th>
<th>Area involved</th>
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<td>M/64</td>
<td>UDM*</td>
<td>Ethmoid, maxilla, orbit, sphenoid</td>
<td>Facial swelling, dysesthesia, pain -Paresthesia, loss of vision -Nasal crusting, discharge, necrosis of the turbinate, cranial nerve palsy -Headache 3-10 d before hospitalization -Fever and chills</td>
<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (negative)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
<td>Expired</td>
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<td>2</td>
<td>F/28</td>
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<td>Ethmoid, maxilla, sphenoid</td>
<td>Nasal crusting, discharge, necrosis of the turbinate -Cranial nerve palsy -Headache 3-10 d before hospitalization -Fever</td>
<td>H&amp;E and PAS (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (negative)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
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<td>3</td>
<td>F/54</td>
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<td>Nose, maxilla, hard palate, orbit</td>
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<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (negative)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
<td>Expired</td>
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<td>F/60</td>
<td>AML, C</td>
<td>Nose, maxilla, medial concha, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain -Nasal crusting, discharge, necrosis of the turbinate -Cranial nerve palsy</td>
<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (Mucor spp.)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
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<td>Not performed</td>
<td>Direct smear (asceptate hyphae) Culture (negative)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
<td>Cured</td>
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<td>6</td>
<td>F/61</td>
<td>UDM</td>
<td>Nose, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain -Nasal crusting, discharge, necrosis of the turbinate -Cranial nerve palsy</td>
<td>H&amp;E and PAS (asceptate hyphae)</td>
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<td>Cured</td>
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<td>7</td>
<td>M/47</td>
<td>UDM</td>
<td>Maxilla, posterior turbinate, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain</td>
<td>H&amp;E (asceptate hyphae)</td>
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<td>H&amp;E (asceptate hyphae)</td>
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<td>Sino-nasal debridement</td>
<td>Cured</td>
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<td>9</td>
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<td>UDM</td>
<td>Ethmoid, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain</td>
<td>H&amp;E and PAS (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (not performed)</td>
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<tr>
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<td>F/61</td>
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<td>Maxilla, nose, hard palate, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain -Nasal crusting, discharge, necrosis of the turbinate -Palatal necrosis -Cranial nerve palsy -Headache 3-10 d before hospitalization</td>
<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (Mucor spp.)</td>
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<td>Expired</td>
</tr>
<tr>
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<td>Ethmoid, sphenoid</td>
<td>Facial swelling, dysesthesia, and pain</td>
<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (Rhizopus spp.)</td>
<td>Sino-nasal debridement + medical treatment with cAMB</td>
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<tr>
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<td>F/56</td>
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<td>Ethmoid, maxilla, orbit</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain -Nasal crusting, discharge, necrosis of the turbinate -Fever and chills</td>
<td>H&amp;E and PAS (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (negative)</td>
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<td>Cured</td>
</tr>
<tr>
<td>13</td>
<td>M/53</td>
<td>UDM</td>
<td>Ethmoid, maxilla, orbit</td>
<td>Paresthesia, propitious, loss of vision, chemosensory pain -Cranial nerve palsy -Headache 3-10 d before hospitalization</td>
<td>H&amp;E (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (Mucor spp.)</td>
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<tr>
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<td>F/52</td>
<td>UDM</td>
<td>Maxilla, orbit</td>
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<td>H&amp;E (asceptate hyphae)</td>
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<td>Sino-nasal debridement + medical treatment with cAMB</td>
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<tr>
<td>15</td>
<td>F/33</td>
<td>UDM</td>
<td>Maxilla, orbit, nose</td>
<td>Facial swelling, dysesthesia, and pain -Paresthesia, propitious, loss of vision, pain</td>
<td>H&amp;E and PAS (asceptate hyphae)</td>
<td>Direct smear (asceptate hyphae) Culture (Mucor spp.)</td>
<td>Sino-nasal debridement + Orbital exenteration + Medical treatment with cAMB</td>
<td>Cured</td>
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*UDM: uncontrolled diabetes mellitus; BT: beta-thalassemia; AML: acute myeloid leukemia; MT: malignant T-cell lymphoma; D: deferoxamine therapy; C: chemotherapy; cAMB: conventional amphotericin B

evident in 12 (80%) patients. Nasal discharge, crust, and necrosis of the turbinate were present in nine (60%) patients. Eight (53.3%) patients had a headache 3–10 days prior to hospital admission. Fever was present in three (20%) cases and was accompanied with chills and dizziness in two (13.3%) cases. Ear pain and itching were evident in two (13.3%) cases.

Four (26.7%) patients had history of tooth extraction before the onset of disease manifestations (case no. 3: three weeks before; and cases no. 2, 7, and 13: one week before the onset of manifestations). Two (13.3%) patients had history of surgery (case no. 9: two sinus surgeries; and case no. 13: a cataract surgery eight months before the onset of manifestations). FESS was conducted in all the patients and biopsies of the mucosa were obtained from the involved areas under endoscopic visualization. Diagnosis in 5/15 (33.3%) of the cases was confirmed by culture and in 8/15 (53.3%) cases, no growth in culture was noted (Table 1). Amphotericin B in combination with surgical debridement was used in the treatment of 80% of the cases.

Furthermore, 11 out of 15 (73.3%) patients who were diagnosed early and underwent medical and extensive surgical debridement of the infected tissues survived. Conventional amphotericin B (cAMB) treatment (average total dose of 50 mg/day) was administered for 5-31 days. Patients at an advanced stage of the disease at the time of diagnosis received the shortest periods of treatment. Despite the initiation of the treatment, these patients deteriorated rapidly and died shortly. Curative surgical interventions, such as ethmoidectomy, sphenoidectomy, septectomy, and maxillary antrostomy, were applied in nine patients (60%; cases no. 1–5 and 10–13). Debridement of tissue and polypotomy were performed in two (13.3%) patients (cases no. 7 and 8); ethmoid suction was performed in cases no. 9 and 14 (Table 1).

Three out of 15 (20%) patients (cases no. 7–9) were diagnosed at an early stage and cured only with surgical debridement of the affected tissues through FESS; in case no. 7, the ethmoid sinus was not affected and the right maxillary sinus was turbid and polypoid. In case no. 8, turbidity was observed in the medial concha; patient no. 9 had extensive bloody nasal discharge with ethmoid involvement and underwent right ethmoidectomy and antrostomy. Despite medical and surgical treatment, 4 out of 15 (26.6%) patients died (cases no. 1–3, and 10).

**Discussion**

Fungal infections caused by the members of the order Mucorales (i.e., mucormycosis) are characterized by severe morbidity and high mortality [19]. These life-threatening infections develop expeditiously and spread by a rapid angioinvasion, causing thrombosis of the blood vessels and tissue necrosis in immunocompromised hosts [22]. The annual incidence of mucormycosis is 1.7 per 1,000,000 individuals [23]. The disease rarely affects healthy individuals [24]. In patients suffering from mucormycosis, the involvement is most commonly rhino orbital cerebral (33–49%), cutaneous (10–16%), pulmonary (10–11%), disseminated (6–12%), or gastrointestinal (2–11%) [23]. ROCM refers to infection of the nose and sinuses, with a critical involvement of the eye and cranial structures [25].

**Predisposing factors and pathogenesis**

The majority (86.7%) of our cases had uncontrolled diabetes; one of these patients had beta-thalassemia major and suffered from secondary diabetes mellitus because of iron overload and was receiving iron chelation therapy for years. Moreover, 13.3% of the cases had a hematological malignancy and were receiving chemotherapy for 18 months, which resulted in functional and/or quantitative deficiencies in neutrophils and macrophages, as well as susceptibility to mucormycosis.

In line with our study, other studies also showed that diabetes mellitus is the main underlying condition of ROCM followed by hematological disorders and transplantation due to chemotherapy causing immune defects [1, 3, 5, 9, 26–29]. In a study of 98 cases of mucormycosis in Iran, Vaezi et al. [29] reported that uncontrolled diabetes was the most common underlying condition. Pak et al. [28] stated that in 40% of all cases of mucormycosis, diabetes mellitus was the most common underlying disease present in 70% of rhino cerebral mucormycosis cases. In review of 929 mucormycosis cases, Roden et al. [3] also ascribed that diabetes was the main predisposing factor. Mane et al. [30] reported 13 cases of ROCM with diabetes as the underlying disease in all of them. Sachdeva et al. [31] described six cases of ROCM all of whom had diabetes.

The Mucoralean fungi are highly common in nature. Their spores are widespread and found in decaying foods, plants, and soil. The most common route of entry of sporangiospores is via respiration. After sporangiospore inhalation, the spores enter the nose, settle on the nasal turbinate, and may germinate to form hyphae and invade the tissues in immunocompromised hosts and patients with uncontrolled diabetes [32]. In uncontrolled diabetes
patients with ketoacidosis, neutrophil functions including chemotaxis, adherence, and oxidative burst are impaired [33–36], thereby failing to damage the hyphae. Uncontrolled diabetes generates favorable conditions facilitating the growth of Rhizopus oryzae, a common agent of mucormycosis; this organism produces keto-reductase as a virulence factor that enables them to grow in the acidic and glucose-rich environment generated in ketoacidosis states [37].

Mucoralean fungi have a remarkable affinity for small- and medium-sized arteries and penetrate the internal elastic lamina, causing endothelial damage, thrombosis, and tissue infarction [38]. In a healthy host, tissue macrophages and functional neutrophils effectively respond to the sporangiospores and hyphal elements of the Mucoralean fungi. Macrophages digest and kill the spores by non-oxidative mechanisms [32, 39] and neutrophils damage the hyphae by releasing the contents of their granules, thereby preventing fungal invasion of the surrounding tissues [40].

In the current study, 20% of the patients with ROCM were associated with hematologic disorders such as AML and T-cell lymphoma. Chemotherapy-induced neutropenia has led to an increase in the incidence of ROCM in patients with hematologic malignancy. Quantitative and qualitative abnormalities in neutrophils and macrophages result in elevated risk of mucormycosis [3]. In addition, one patient in the current study had beta-thalassemia major and secondary diabetes mellitus. Iron overload associated with blood transfusion enhanced the risk of mucormycosis.

Members of the order Mucorales are ferrophilic. High glycosylation of proteins, such as transferrin and ferritin, results in a decreased affinity of these proteins for iron, making free iron available to the microorganisms [41–45]. The importance of iron in the pathogenesis of mucormycosis was described in several studies on chronic deferoxamine therapy and iron overload states. Deferoxamine acts as a siderophore for the Mucorales fungi and increases their iron uptake, and in turn, enhances hyphal growth [46–50].

**Common mucormycosis agents**

In the present study, only 33.3% of the cases were confirmed by culture. As a caveat, the report of the causative agents may be unreliable because more than half of the cases were culture-negative and were unconfirmed by molecular methods. Recovery rate of zygomycetes in culture is considerably low [19]. Low recovery might be as a result of few viable fungal elements, delay in culturing, long storage in refrigerator, and high manipulation (grinding) of tissue samples [51]. According to several reports, the most common cause of mucormycosis is *R. oryzae*, followed by *Mucor, Cunninghamella, Apophysomyces*, and *Lichtheimia* species [8–11, 12, 28, 52].

**The extent and typical clinical presentations**

In this study, ptosis and ophthalmoplegia (13/15 or 86.7%) as well as facial involvement symptoms (12/15 or 80.0%) were the typical manifestations. Cutaneous or mucosal necrosis, facial palsy, and diplopia are noted in late stages of the disease [53]. These were apparent in four of our cases, all with paranasal sinus involvement; prognosis was poor and these patients died of infection.

In agreement with our findings, there are several reports on the most common manifestations of mucormycosis in ROCM patients indicating ptosis, proptosis, periorbital swelling, facial swelling, and dysesthesia on the involved side and black necrotic area in the turbinate, palate, and other involved sites [1–4, 6, 7, 9, 12, 30, 32].

The disease usually starts in the nasal mucosa, turbinate, or palate and spreads to the paranasal sinuses; it spreads to the retro-orbital region via the ethmoid sinus. Kulkarni et al. [38] proposed that the fungi enter the anterior ethmoidal sinus, which could not have any presentations until they spread to the orbit. Additionally, the cribriform plate and the roof of the orbit are very thin and could be portal of entry to the intracerebral area. The disease may also progress through the retro-orbital region or cause sphenoid sinus involvement. Sadr-Hosseini et al. [54] reported that although the intracranial spread of fungi can occur via several routes, the pterygopalatine space is the main portal of entry in the majority of cases. The authors determined that the disease spread to the orbit and soft facial tissue from pterygopalatine space, and then through the inferior orbital fissure, extend to the retro-global area of the orbit, resulting in ophthalmic manifestations. Pterygopalatine involvement was also reported in other studies [55–57].

Similarly, Pillsbury and Fischer [58] proposed that the infection begins in the nose and spreads to the paranasal sinuses and orbit, and after invading the orbit, it can reach the central nervous system (CNS) tissue. Diplopia and ophthalmoplegia are the initial findings of the cavernous sinus involvement, which are observed before any alterations are apparent by diagnostic imaging. When entering posteriorly to the optic foramen, these fungi cause edema, inflammation, necrosis, and damage to the ophthalmic artery and optic nerves. The orbital
apex syndrome may therefore manifest by chemosis, ptosis, proptosis, loss of vision, and blindness [59, 60]. Bhadada et al. [53] reported six patients with ROCM and type I diabetes mellitus. They indicated proptosis and ptosis as the most common symptoms. Yohai et al. [14] and Ferry et al. [16] reported proptosis and ophthalmoplegia in the majority of their patients.

**Diagnosis**

Definitive diagnosis is based on histopathological examination of biopsy specimens from the involved area. In the present study, a similar approach was used successfully in all the patients. The Mucoralean fungi appear as broad aseptate hyphae, 10–50 μm in size, with right angle branching [61]. Histological evaluation is considered more sensitive than culturing [62, 63].

Imaging is very important and useful for assessing the extent of disease. CT scanning provides evidence for the thickening of the mucosa and turbidity in the sinuses. Infection spread to the orbit and cranial area can be evaluated by magnetic resonance imaging (MRI) [64]. Opacification of the paranasal sinuses is the principal radiographic finding concerning the sinuses during mucormycosis. CT scanning may also reveal fluid levels, bone destruction, and osteomyelitis [65–67].

To prevent spread of infection to the orbit compartment, early diagnosis of sinusitis in mucormycosis is of great significance. It was shown that even 12 hours delay in diagnosis could be fatal and studies on autopsy reported that 50% of diagnoses were postmortem [68, 69].

All of our cases were confirmed by histological examination of biopsy specimens from sinus endoscopy and broad, coenocytic hyphae were detected. Diagnostic nasal endoscopy was performed on all the patients, and turbidity accompanied by thickening of the involved area was observed.

**Treatment and prognosis**

In the current study, 80% of the patients received medical treatment in addition to surgical debridement of the affected area and survived. The patients were diagnosed at late stages of the disease with an extensive involvement of the sinuses and the treatment was not effective. Ericson et al. [70] reported survival of 80% of the patients receiving medical and surgical treatment. Straus et al. [71] reported 40% survival of patients. Mortality rate is high in patients with CNS involvement in initial examination [72]. In ROCM, delayed diagnosis and treatment leads to facial necrosis, bilateral sinus involvement, and hemiparesis [14].

Endoscopic sinus surgery may help patients with focal and localized disease and is associated with low morbidity [73]. The main approaches to the treatment of ROCM include management of hyperglycemia and acidosis, systemic anti-fungal therapy with amphotericin B, and immediate aggressive surgical resection of the involved area. The granulocyte colony-stimulating factor (G-CSF) may help reconstitute host defense; hyperbaric oxygen can inhibit the growth of microorganisms by reducing tissue hypoxia [65, 68].

Curative surgical procedures, both endoscopic and open techniques, are utilized to debride the whole necrotic tissues. These modalities include Caldwell-Luc, medial or radical ethmoidectomy, maxillectomy, sphenoidectomy, and even orbital exenteration, depending on the involved area. Medical management alone is not effective since vascular thrombosis results in poor drug delivery to the site of infection. Prognosis is directly associated with time interval before diagnosis and treatment. Early diagnosis and initiation of proper treatment are extremely important for successful eradication of the infection and patient survival. Teamwork, with the involvement of highly skilled ENT surgeons, neurologists, ophthalmologists, and dental specialists is critical in the management of ROCM patients [69, 73].

**Conclusion**

The prevalence of diabetes in developing countries, as a common risk factor for ROCM, has led to an increase in the incidence of ROCM. Health care surveillance programs, awareness of the clinicians, and cooperation of mycologists and pathologists can lead to early and accurate diagnosis and facilitate management of this devastating infection. Patients with hematological malignancies presenting with periorbital pain and swelling or blood-stained nasal discharge poorly respond to prolonged antibiotic therapy and multiple cranial nerve palsy and should raise the suspicion of ROCM.

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**Author’s contribution**

contributed to data analysis and interpretation; A.A., T.S., and M.D wrote the main manuscript; A.A., T.S., and M.I revised the first draft of the manuscript; R.P., AM.K, SJ.M, M.G, SA. M, M.N, M.G, and L.V acquired data. All the authors reviewed the manuscript.

Conflicts of interest

None declared.

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