

# Rhino-Orbito-Cerebral Mucormycosis: A Case Report and Review of the Literature

## SUMMARY

*Rhino-orbito-cerebral mucormycosis is a rare, opportunistic and often fatal fungal infection usually occurring in immuno-compromised or diabetic patients. The treatment involves administration of Amphotericin B and surgical debridement. Due to its lethal nature, early recognition of the infection is essential.*

*This paper reports a case of rhino-orbito-cerebral mucormycosis, which developed in a 60-year-old female patient with latent diabetes mellitus after a tooth extraction. The patient, unfortunately, succumbed due to the delayed diagnosis. This case study is combined with a review of the literature.*

**Keywords:** Mucormycosis; Diabetes Mellitus

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**CASE REPORT (CR)**

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## Introduction

Rhino-orbital-cerebral mucormycosis (ROCM) is an acute, opportunistic, often fatal fungal infection occurring mainly in diabetics, particularly those with ketoacidosis. Other predisposing factors include leukemia, lymphoma, disseminated neoplasms, extensive burn injuries and prolonged corticosteroid or immuno-suppressive therapy.

The disease provokes diffuse tissue necrosis. The fungi invade the walls of blood vessels, causing thrombosis and ischemia. Progression of the disease is rapid and intracranial dissemination may become fatal. The disease presents symptoms of sinusitis, nasal ulceration and palatal necrosis, while orbital invasion may lead to ophthalmoplegia, proptosis, vision loss, and chemosis. Further progression of the disease may result in cerebral involvement with poor prognosis.

The principles of management comprise a high index of suspicion, early diagnosis and combined treatment with Amphotericin B and aggressive surgical debridement. Hyperbaric oxygen therapy has also been reported<sup>5,37,50</sup>.

The following report presents a case of ROCM, which developed in a patient with latent diabetes who unfortunately succumbed. A review of the literature is also presented.

## Case Report

A 60-year-old female patient was admitted to “G. Papanikolaou” General hospital 2 days after a tooth extraction, with headache, malaise, left mid-facial pain, erythema, swelling and an abscess in the buccal vestibule resistant to surgical drainage. The patient was well-oriented and her vital signs were stable. Her past medical history was not significant, but laboratory examination immediately after the admission revealed uncontrolled diabetes. White blood cells were 18000 per mm<sup>3</sup>, the blood glucose level 380 mg/dl, while the urine analysis showed 3+ for glucose and ketones.

Within 14 hours the patient’s clinical picture deteriorated significantly. Physical examination showed left periorbital cellulitis, chemosis, a dilated left pupil non-reactive to light, proptosis with limited movement, and decreased vision acuity of the left eye (Fig. 1). Examination of the nasal cavity showed nothing significant, but the following day a necrotic lesion on the left side of the hard palate was revealed during oral examination. The patient rapidly developed necrotic lesions in the nose, upper lip and left infraorbital area, while chemosis and erythema progressively extended to the right side (Fig. 2). CT scan disclosed occupation of the left maxillary sinus,

a perforated hard palate, and oedema of the left orbit, however, without any significant intracranial findings.

polymorphonuclear cells in the cerebrospinal fluid. The patient was finally intubated and admitted to the intensive care unit, where empiric treatment was given with intravenous metronidazole (500mg, 3 times daily), vancomycin (1gr, twice daily) and ceftriaxone (1gr, twice daily).



Figure 1. Presentation of the patient 14 hours after the admission and the drainage of the abscess

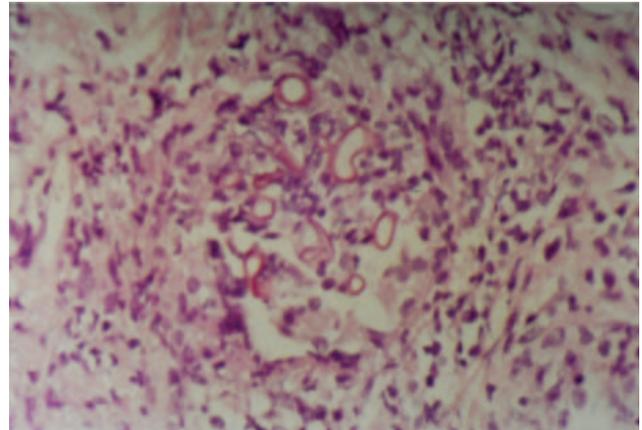


Figure 3. Photomicrographs showing non-septate right-angled branching hyphae of mucormycosis in the ground of necrotic tissue (HE, 40x10)



Figure 2. Progressing chemosis and erythema of the left eye, expanding to the right eye. Necrotic lesions in the nose, upper lip and infraorbital area



Figure 4. Final picture of the patient in the intensive care unit. Note the extensive necrotic lesions in the left orbit, cheek, nose and the lips and the chemosis and erythema covering almost all the face

The patient became progressively disoriented, presenting neck rigidity. Lumbar puncture was performed revealing cerebral involvement with a large count of

A biopsy of the vestibule was performed. The histopathological findings revealed non-septate fungal hyphae consistent with mucormycosis (Fig. 3); the triple antibiotic scheme was stopped and Amphotericin B (0.25 mg/kg daily) was administered. However, the patient did not respond to the treatment. During the following 2 days the left eye became more proptotic and the facial necrosis rapidly spread, extending to the right side (Fig. 4). The neurological picture gradually deteriorated and the patient manifested renal failure and sepsis before unfortunately succumbing.

## Discussion

ROCM is an acute opportunistic fatal fungal infection caused by the species *Rhizopus*, *Rhizomucor* and *Absidia*<sup>17,42,47</sup>. These saprophytic fungi can be found in soil, bread mould, rotten fruit and vegetables<sup>3,36,38,39,49,50</sup>, and seem to infect humans with compromised systemic health. The disease most commonly originates in the oral and nasal mucosa where in healthy individuals the spores normally parasitize, but are prevented from development by the mechanism of phagocytosis. In immuno-compromised patients this mechanism fails, resulting in the development of the infection.

The fungi show a remarkable affinity for arteries and grow along the internal elastic lamina causing thrombosis, ischemia and infarction<sup>6,19,20,22</sup>. The infection spreads from the oral and nasal cavity to the paranasal sinuses and enters the orbit *via* the ethmoid and maxillary sinuses, or through the nasolacrimal duct<sup>2</sup>. Further progression may lead to intra-cerebral extension from the orbit *via* the orbital apex, orbital vessels or *via* cribriform plate<sup>2</sup>. Diabetes, especially uncontrolled, predisposes to this infection<sup>8,19,28,38,50</sup>. The iron and glucose rich acidic environment in diabetics creates suitable conditions for fungal proliferation<sup>14,50</sup>. Other factors predisposing to mucormycosis include haematological malignancies, extensive burn injuries, chemotherapy, transplantation, prolonged corticosteroid or immuno-suppressive therapy and, rarely, AIDS<sup>10,25,34,40,41,47</sup>. Also, patients under deferoxamine therapy should be highly suspect for mucormycosis as deferoxamine provides iron to Mucorales, facilitating their growth<sup>11-13,16,33,45</sup>.

ROCM presents with a characteristic clinical picture, consisting of fever, malaise, sinusitis, chemosis, black nasal eschar, peri-orbital cellulites, and palatal necrosis. Paranasal sinuses were involved in all patients<sup>7</sup> while sinus involvement was found in 69% and 79% according to other authors<sup>19,50</sup>. As the infection progresses to the orbit, the patient manifests ophthalmoplegia, proptosis, chemosis, vision loss due to ischemic necrosis of the intraorbital cranial nerves, orbital cellulites or ocular invasion of the mucorales<sup>4,9,43,48,50</sup>. Intracranial extension presents with

altered sensorium, hemiparesis and meningeal signs<sup>40</sup>. Patients with keto-acidosis whose clinical picture does not improve after appropriate treatment, may suggest mucormycosis<sup>28</sup>. Cavemous sinus thrombosis results from spread of infection from the orbit and presents with early vision loss. Internal carotid artery thrombosis is a rare complication leading to cerebral ischemia and infarction.

Diagnosis can be made by direct microscopy, histopathological examination or by culturing on Sabroud's agar. Cultures are often negative, but this should not affect treatment and prognosis<sup>47,50</sup>. The fungi can be easily detected as aseptate hyphae with right-angled branching on Haematoxylin and Eosin stained sections; with periodic acid-Schiff reaction; or by Grocott-Gomoni methenamine silver nitrate stained section<sup>1,8,29,40,44,37</sup>. The predominant histological findings are ischemia and haemorrhaging necrosis, moderate suppurative inflammation and vascular thrombosis<sup>8,29,44</sup>. Plain orbit or sinus radiography are non-specific, while CT or MRI are useful imaging modalities for evaluating the extension of the disease.

Initial cerebritis is presented with bifrontal lucencies without mass. Abscess formation and bone destruction can be easily detected<sup>1,8,24</sup>. In areas of anatomic complexity, where CT or MRI are not helpful, angiography or surgical exploration should be performed<sup>1,15,23</sup>. Cerebrospinal fluid findings are usually non specific and blood cultures are rarely positive<sup>35</sup>.

The treatment of ROCM includes correction of any underlying disorder, administration of Amphotericin B, and prompt surgical intervention<sup>1</sup>. In diabetics, management of the keto-acidosis and dehydration improve overall survival rate, while the management of the immuno-suppressed patients is more difficult to achieve. Hyperbaric oxygen therapy has been reported as an adjunctive modality<sup>5,48</sup>, as it not only exerts a fungistatic effect but also boosts neovascularization<sup>30,31,37</sup>.

Amphotericin B is a fungostatic agent that is usually ineffective in eradicating the primary lesion, but it can control early micro-metastases<sup>41</sup>. Doses of 0.7-1 mg/kg/day are usually recommended<sup>26</sup>. In the past, Amphotericin B was administered after a test dose and, depending on the patient's response, the dosage could be gradually increased. In cases of rapid progression, a sharp increase is recommended if the degree of adverse reaction is tolerated<sup>48</sup>. Medication side-effects are fever, headaches, nausea, vomiting, hypokalemia, thrombophlebitis, azotemia and renal dysfunction. The last years Liposomal Amphotericin B replaced conventional Amphotericin B, as it is less nephrotoxic and may enhance delivery properties to infected areas<sup>21,40</sup>. The lethal dose (LD50) is 10-15 higher than that of conventional Amphotericin B<sup>27</sup>. The recommended dose can be raised to 5mg/kg/day.

Extensive surgical debridement enhances survival rate and is necessary except in cases with terminal neoplasms<sup>1</sup>. Orbital exenteration is required in patients with ocular involvement or signs of retinal artery thrombosis<sup>8</sup>.

Prognosis depends on the nature of the underlying disease, early diagnosis and prompt management<sup>1</sup>. Diabetics seem to have a better survival rate<sup>1,8</sup>. Indicators of poor prognosis are hemiparesis or hemiplegia, bilateral infection, renal disease leukaemia, deferoxamine therapy, palatal and facial necrosis<sup>8,48,50</sup>. Considering the fact that even when appropriate treatment is instituted, only about half of the ROCM cases survive, it can be easily concluded that early diagnosis and immediate, aggressive treatment are of great importance.

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