CASE REPORT

Paranasal Mucormycosis in an Immunocompetent Individual: Importance of Early Diagnosis

Abhishek Soni

Senior Lecturer, Dept. of Oral Medicine & Radiology, Modern Dental College & Research Center, Opp. Gandhi Nagar, Airport Road, Indore (Madhya Pradesh, India); Pin- 453112 (Correspondence Address). Contact Us: www.ijohmr.com.

ABSTRACT

Paranasal mucormycosis is one of the most rapidly progressing and lethal form of fungal infection with a characteristic destruction and necrosis, especially in immunocompromised patients. Since mucormycosis occurs infrequently in apparently healthy (immunocompetent) individuals, it may pose a diagnostic challenge and therapeutic dilemma for the clinicians who are unfamiliar with its clinical presentation. The presented clinical case report was extremely unusual as mucormycosis infection affects the immunocompetent patient with the mere finding of oroantral communication secondary to traumatic extraction. In the presented case, the mucormycosis infection followed a chronic course, and in a somewhat indolent form which eventually caused maxillary necrosis. This accentuated the need to include this fatal opportunistic fungal infection in the differential diagnosis of maxillary lesions in otherwise healthy patients showing minimal clinical signs and symptoms. The purpose of this paper is to draw attention to the clinical presentation and pathogenesis of mucormycosis infection and to highlight the need for early diagnosis and prompt treatment of this potentially fatal fungal infection.

KEYWORDS: Mucormycosis, early diagnosis, paranasal sinus disease, maxilla, opportunistic infection, fungal sinusitis.

INTRODUCTION

Fungal infection of the paranasal sinuses is an increasingly recognized entity both in immune-compromised and immunocompetent individuals. Of all the fungal infections, Aspergillosis and Mucormycosis are the most common invasive fungal infection which has propensity to involve the maxillary sinus.[1] Mucormycosis is considered as one of the most important medical complications in immunocompromised patients, especially diabetics.[2,3] It rarely affects apparently healthy (immunocompetent) people.[4]

Mucormycosis is caused by fungi of the class Zygomycetes, and it represents 8.3-13.0% of all fungal infections which is commonly cultured from the nose, throat, mouth, and feces.[5] The most important species in order of frequency is *Rhizopus arrhizus (oryzae)*.[6] Based on clinical presentation, five major clinical forms of mucormycosis have been described in the literature, which includes rhino-orbito-cerebral form (44-49%), being the most common clinical presentation, followed by cutaneous form (10-16%), pulmonary form (10-11%), disseminated form(6-11.6%), and gastrointestinal (2-11%) form.[7]

Early diagnosis is important in such infections because the delay in the diagnosis and prompt treatment can be life-threatening due to the ability of the fungi to invade adjacent blood vessels and embolize to distant organs including the brain. Computed tomography (CT) with axial and coronal sections is a highly accurate and noninvasive modality of accurately imaging sinonasal mycosis.[8] This article report a clinical case to highlight the importance of early diagnosis and stepwise diagnostic approach in evaluating a case of paranasal mucormycosis infection in an immunocompetent patient showing minimal clinical signs and symptoms which could concealed its presence. This paper also attempts to emphasize the need for advanced imaging technique in such dilemmatic condition which is imperative in managing such invasive fungal sinusitis so as to avoid the potentially fatal complications in clinical settings.

CASE REPORT

A thirty-one-year-old male patient reported to the outpatient department with a chief complaint of pain and swelling on left middle one-third of the face since two months. Detailed history revealed that the patient had suffered from persistent headache and heaviness on left side of the face, six months back. The pre-treatment radiographs (panoramic radiograph and paranasal sinus view) revealed partial opacification of the left maxillary sinus with a displaced left maxillary third molar in the antrum (Figure 1). The patient had undergone surgical extraction of the same along with the removal of a carious first molar on the same side. Following extraction, the socket did not heal completely, and patient repeatedly experienced dull aching pain and pus discharge from the extraction site. Due to deteriorated dental condition and no relief in symptoms, the patient reported to the department. There was no history of fever, paresthesia, orbital pain, diplopia, and rhinorrhea. Past

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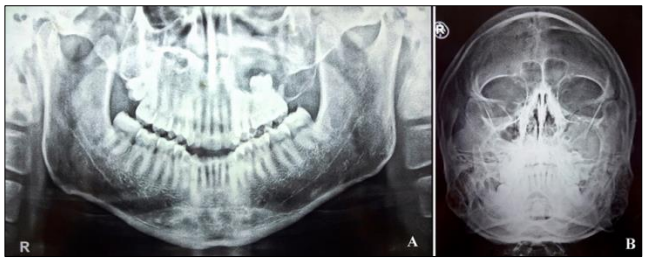

Figure 1 (A) Pre-treatment panoramic radiograph and (B) Pre-treatment paranasal sinus view revealed partial opacification of the left maxillary sinus with a displaced left maxillary third molar in the antrum

medical history was non-contributory.

On extraoral examination, a diffuse, firm, tender swelling was evident involving the left middle third of face causing obliteration of nasolabial fold. Intraoral examination revealed a large oroantral communication about 0.5 cm in diameter in the left maxillary posterior region, with evidence of foul discharge at the site of extracted molar along with the exposed bony socket (Figure 2).

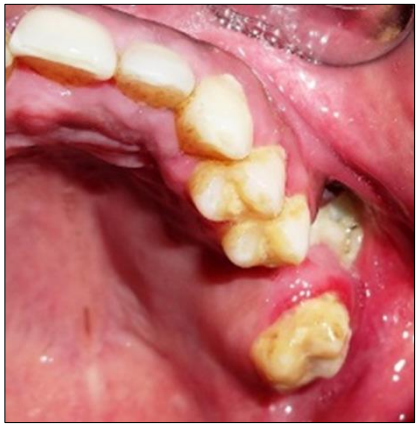

Figure 2 Intraoral picture showing large oro-antral communication with pus discharge at the site of extracted tooth

A panoramic radiograph revealed partial opacification of the lumen of the left maxillary sinus. The discontinuity in the floor of the maxillary sinus on the left side was also noted (Figure 3). Considering the large bony defect with communication deep in the maxillary sinus, the patient was subjected to computed tomography (CT) scan. CT scan revealed a non-homogenous opacification of the left maxillary sinus, causing obstruction of the left osteo-meatal complex extending into the middle meatus,

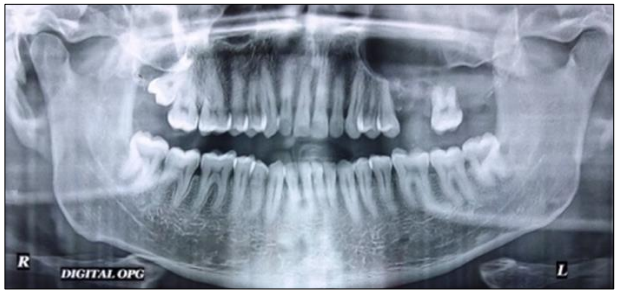

Figure 3 Panoramic radiograph showing a large, well-defined unilocular hazy radiopaque shadow occupying the lumen of the left maxillary sinus with discontinuity in the floor of the sinus.

ethmoidal, frontal and sphenoidal sinus. There was thinning and erosion of medial, posterolateral and inferolateral bony wall of the left maxillary sinus along with the prominent erosion of alveolus process of the maxilla (Figure 4). No intraorbital extension of the lesion was noted.

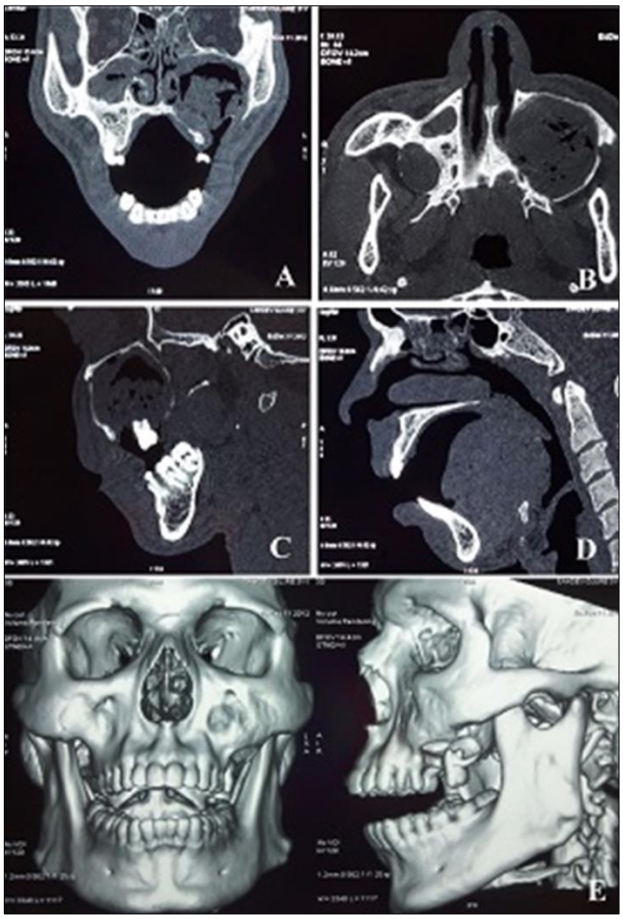

Figure 4 (A, B, C) CT sections (coronal, axial and sagittal) depict a well-defined expansile, cystic lesion measuring approximately 4.6 x 3.8 x 4.5 cms, involving the left maxillary sinus region. Thinning and erosion of the medial, postero-lateral and infero-lateral bony wall along with prominent erosion of alveolus process of maxilla was evident. An irregular soft tissue shadow was seen, occupying the walls and the lumen of the cystic cavity with multiple air pockets, along with the obliterated osteomeatal complex on the left side. Involvement of ethmoidal sinus was also evident due to mucosal thickening; (D) CT section (sagittal) depicts the involvement of sphenoidal sinus; (E) 3D reconstruction depicting the destruction of the left alveolar process of maxilla in the posterior region along with the expansion of cortex.

Scrape Cytology from the exposed bony wall of the socket revealed fungal hyphae with neutrophils infiltration, and generalized chronic inflammatory cell infiltrate. Hyphae were aseptate, broad, dichotomous branching at 90^{o} angle, suggestive of mucormycosis (Figure 5). Cultures grown in Sabouraud's Dextrose Agar medium showed cotton wool growth of Mucor.

The patient was first subjected to vigorous antifungal therapy [Itraconazole 100mg (Fungitrace)], and antibacterial therapy [Levofloxacillin 500mg (Mucosyn)] for ten days, followed by wide surgical debridement of the involved dead and infected tissue. Amphotericin-B

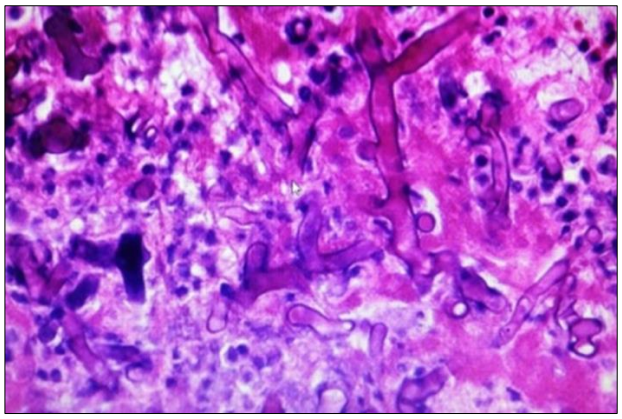

Figure 5 Hematoxylin & Eosin stained section (40X) showing broad, aseptate fungal hyphae dichotomously branched at 90° angles suggestive of mucormycosis

(1mg/kg/day) was administered intravenously by slow infusion over 4–6 hours for 2 weeks. Under general anesthesia, a mucoperiosteal flap was raised, and the hypertrophic mucosal lining that was thickly adhered to the maxillary sinus walls was surgically removed (Figure 6). The region was allowed to heal by secondary intention. On follow-up evaluation after every three months for one year, the healing was found to be uneventful with no complications or recurrence (Figure 7).

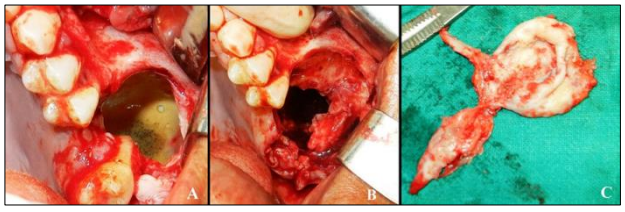

Figure 6 (A,B) Intraoperative picture depicting the surgical removal of hypertrophic mucosal lining that was thickly adhering to the maxillary sinus walls; (C) Tissue specimen showing hypertrophic mucosal lining.

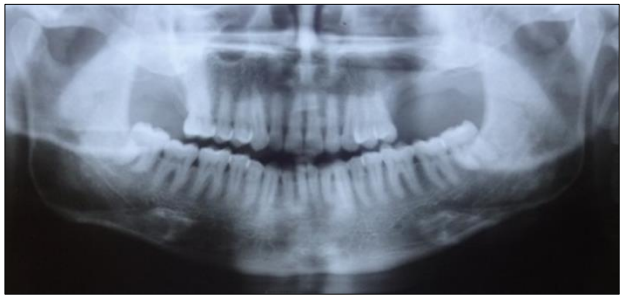

Figure 7 Panoramic radiograph taken one year post-operatively, depicting the progressive lesion resolution with new bone formation in the maxillary sinus region.

DISCUSSION

Mucormycosis is a rare fulminating opportunistic fungal infection caused by a fungus of the order Mucorales.[9,10] It is usually seen in immunocompromised individuals such as in uncontrolled diabetic *mellitus* with ketoacidosis or in association with other debilitating diseases. Its rare occurrence in immunocompetent individuals may be attributed to the presence of intact mucosal epithelium and endothelium which represent an effective barrier against tissue invasion and angioinvasion.[7] However, literature analysis (1978-2009) carried out by Mignogna et al[7] revealed that mucormycosis infection could even affect immunocompetent or otherwise healthy individuals. In fact, the possibility of developing a mucor infection in such patients seems to be related to the ability of this fungus to attack the epithelium previously damaged by prior infection, cytotoxic agent or direct trauma.[11] Auluck[12] observed that immunocompromised or immunosuppressed patient having bone necrosis following tooth extraction should alert a clinician of possible mucormycotic infection. It is also suggested that mucor sporangiospores are able to secrete several toxins or proteases, which has capacity to directly destroy the endothelial cells in the mucosal membranes.[11] In addition to this, a chronic local insult, such as chronic sinusitis, may also lead to the development of mucor infection in these individuals. It has been speculated that an impairment of mucociliary clearance or loss of immune defense due to chronic sinusitis may lead to alteration of first-line barrier defense of sinus mucosa which would render the individual more vulnerable to fungal colonization.[13] Furthermore, in patients with chronic sinusitis, there is reduction of certain important molecules such as S100, SPINK5, and members of epidermal differentiation complex, which are imperative in maintaining the barrier function in the upper airways and sinuses.[14]

In immunocompetent patients, the major source of infection considered to be the nose and maxillary sinuses. Once the infection has colonized the nose and the paranasal sinuses, these fungi has propensity to erode the bony wall and invade the small blood vessels, leading to thrombosis, ischemia, and tissue necrosis. Involvement of the oral cavity, predominantly the hard palate, is usually common with presenting symptoms of pain, nasal discharge, and foul smell with black necrotic oral ulceration.[5,7,15,16] From the palate and nasal mucosa, the infection may progress to involve the base of the skull through blood vessels, disseminating to the central nervous system. It may have tendency to further involve the cranial nerves, especially cranial nerve II, III, IV, and VI leading to their functional impairment. Involvement of the cavernous sinus via hematogenous spread also have been reported resulting in cavernous sinus thrombosis.[17,18] They may spread everywhere in the body, giving the disseminated form.[5] In our case, mucormycosis infection affect an immunocompetent host and it has been hypothesized that in the present case, chronic sinusitis was a favorable condition to harbor the mucor fungi in the damaged epithelium of the sinus. Infection would have eroded bone through walls of the sinus and remained localized, that might have resulted in a local immunosuppression, thus fostering the development of an invasive fungal infection. The situation may get worsened after the patient had undergone the traumatic extraction.

Paranasal mycoses occur in two distinct forms. A benign or non-invasive infection which is seen in immune-

competent individuals and presents as fractious sinusitis and nasal polyposis that fails to respond to repeated courses of antibiotics. It has a slow mild course with no tissue invasion, expansion or erosion of the sinus walls. Another is more serious invasive form is usually associated with immunocompromised patient such as poorly controlled diabetic and is usually characterized by its rapid onset and its ability to invade tissues and cause destruction.[5,8]

On plain film radiography, mucormycosis is characterized by focal destruction of the bony walls of the nasal cavity, with hazy radiopaque shadow suggesting the soft-tissue densities in the adjacent ethmoidal and maxillary sinuses.[19,20] Computed Tomography (CT) scan is contemplated as 100% sensitive and 78% specific modality, which is useful in the diagnosis of sinonasal mycosis.[8,21] It is considered as the more sensitive diagnostic tool than plain radiography, providing information on the extent of these lesions, contributing to diagnosis and preoperative preparation.[1] On CT scan, foci of hyperdensity in the affected sinus are highly suggestive of the fungal disease.[8] Magnetic Resonance Image (MRI) is more sensitive than CT in diagnosing fungal sinusitis.[1] On MRI, fungal infections are often appear as hypointense area, both on T1 and T2-weighted images which is mainly attributed to the solid components of the fungal growth, high protein concentration and the presence of manganese, which is paramagnetic. In the present case also, the routine radiography revealed only limited findings in and around the lesion, but use of CT scan revealed the extent of the underlying destruction following fungal sinusitis.

The radiographic findings of mucormycosis are not always specific, and the process may simulate closely an aggressive tumor.[19,20] A unilateral or bilateral pansinus inflammatory changes such as polypoid mucosal thickening along with the presence of radio-dense foci, in association with the homogenous opacity of the sinus is highly suggestive of a non-invasive mucormycosis infection.[1,8] Aggressive enhancing soft tissue density mass extending beyond the confines of the sinus cavity involving the other paranasal sinus and causing bone erosion may be demonstrated in the invasive form.[8] Similar pattern has been seen in our case.

Histopathologically, mucormycosis is diagnosed by broad, irregularly shaped, non-septate hyphae (budding, dichotomous branching) with right angle branching invading the tissue.[22] They are mostly found in the areas bordering the clinical necrosis, especially within necrotic vessel walls. Frequently, area of infarction secondary to arterial invasion and neutrophilic infiltrate in the necrotic tissue can also be appreciated.[15,16,17,23] Use of a special stains such as Grocott-Gomori methenamine silver stain, periodic acid Schiff, or calcofluor stain revealed the presence of mucormycosis.[24] The Gomori's silver methenamine stain was used to demonstrate the fungal hyphae in the present case.

The clinical differential diagnosis for paranasal mucormycosis includes squamous cell carcinoma of the maxillary sinus, which presents as chronic non-healing ulcers with raised and everted margins causing exposure of underlying bone; and malignant salivary gland tumor arising from the accessory glands of the palate. Other clinical features seen in cases of antral carcinoma are the locoregional pain, swelling, epistaxis, nasal discharge, epiphora, diplopia or numbness. In our case, no such symptoms noted which rules out malignancy. Wegener's granulomatosis is another systemic condition characterized by a necrotizing granulomatous condition of the respiratory tract, widespread vasculitis, and necrotizing glomerulonephritis. Common clinical signs and symptoms include sinusitis, rhinorrhea, nasal stuffiness and epistaxis with or without complaint of fever, arthralgia, and weight loss. Gingiva shows characteristic erythematous hyperplasia. In addition to this, destruction of underlying palatal and alveolar bone may also be seen which leads to the formation of an oro-antral fistula. In our case, an absence of systemic signs and symptoms rules out this condition.[12] From the histopathological point of view, mucormycosis and aspergillosis have close microscopic resemblance, however aspergillosis can be distinguished from mucormycosis on the basis of their pattern of hyphae; aspergillosis has septate branching hyphae, while mucormycotic hyphae has smaller width with prominent acute angulations of the branching hyphae.[25,26]

Mucormycosis may be cured by a combination of surgical debridement of the infected area and systemic administration of antifungals. Aggressive control of the underlying disease with complete debridement (resection-type) of the lesion is needed to halt the progression and elimination of this fatal infection. The subsequent wound is best left open for adequate care and irrigation but may be obturated with an obturator to support speech and feeding.[27] Amphotericin B therapy, administered in 5% Dextrose in water, intravenously at a dose of 1.0-1.5 mg/kg daily, considered being useful in controlling these infections. A lipid formulation of amphotericin B is considered to be more efficacious which maintain high blood levels with lower toxicity.[28] Hyperbaric oxygen therapy can also be used as an adjunctive measure in managing such invasive fungal infections.[22]

CONCLUSION

In summary, it appears reasonable to conclude that paranasal mucormycosis may arise in immunocompetent individuals, so every clinician should be aware of their clinical presentation and their pathophysiological aspect. Its inclusion as part of the differential diagnosis of paranasal sinus disease is important, particularly because not all forms follow a benign course and the prognosis is dependent on early diagnosis.

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