CASE REPORT

Mucormycosis: an atrocious mate of patients with diabetes

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SUMMARY

Mucormycosis also called zygomycosis is a rare infection caused by saprophytic aerobic fungus that belongs to a group of fungi called Mucoromycotina in the order Mucorales. Earlier these fungi were called Zygomycota but this scientific name has recently been changed. Mucormycosis can result in an acute, rapidly advancing and occasionally fatal disease caused by different fungi typically found in the soil and in association with decaying organic matter such as leaves, compost piles or rotten wood. These fungal infections are relatively infrequent; however, they occur in individuals who are debilitated in some major way and occasionally in groups of people with multiple penetrating injuries that are contaminated with soil and water from the environment. Mucormycosis is not contagious and does not spread from person to person.

BACKGROUND

This case is of diagnostic implication.

It is presented to highlight the role of scrupulous intraoral examination in timely diagnosis and thus preventing morbidity.

To discern the role of fluconazole in its treatment.

CASE PRESENTATION

A 63-year-old male patient presented with a chief complaint of pain in the upper back jaw region since 2 months with a history of foul odour and associated with stuffiness and purulent discharge from the right side of the nose, loss of sensation in the infraorbital region and upper lip on the same side. The medical history revealed that the patient was diabetic for the past 20 years and was under insulin therapy. He gave a history of cardiac valvular surgery performed 5 years ago and was on aspirin 150 mg since then. He underwent maxillary sinus surgery with septoplasty for the complaint of nasal stuffiness 6 months ago but the specimen was not sent for histopathological examination. The patient also gave a history of mobile teeth extracted in the first quadrant 2 months ago. He had the habit of chewing pan with slaked lime and smoking tobacco (chutta) for the past 35 years which he discontinued 6 months ago.

After general examination, the patient was found to be moderately built, moderately nourished and afebrile. Extraoral findings revealed paraesthesia in the right half of the upper lip and bilateral inflammatory submandibular lymphadenitis. Intraoral examination revealed denuded necrotic bony

sockets of missing 16 and 17 with a buccal oroantral communication. Grade II mobility was apparent in 14 and 15. There was generalised gingival recession, gross attrition with pulpal involvement of 13, 12, 11, 21, 23, 33, 32 and 31 and extrinsic stains on the teeth (figure 1). Based on the history and clinical presentation, a provisional diagnosis of a deep fungal infection was made with a differential diagnosis of primary malignancy of the right maxilla.

INVESTIGATIONS

The patient's fasting blood glucose level was 90 mg/dl and was seronegative to HIV. Paranasal sinus (PNS) showed haziness in the right maxillary sinus without clear lateral wall of the sinus (figure 2). Intra oral periapical radiograph (IOPA) in relation to extracted 14, 15 and 16 revealed enlarged marrow spaces in the edentulous area (figure 3). Floor of the maxillary sinus is visible as a thin radiopaque line. An occlusal radiograph revealed destruction of the anterior hard palate and maxillary alveolar process from 21 to 18 (figure 4). The section of the denuded bone was sent for histopathological examination and it revealed areas of necrosis with bone marrow spaces crammed with branching, aseptate hyphae demonstrated in H&E, Periodic acid-Schiff (PAS) and Grocott-Gomori's methenamine silver staining (figures 5–8). Short chains of bacterial colonies, clusters of *Staphylococci* and *Micrococci* were also present. These features were suggestive of mucormycosis with superimposed polymicrobial osteomyelitis.

Figure 1 Denuded necrotic bony sockets of missing 16 and 17 with a buccal oroantral communication.

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Figure 2 Paranasal sinus showed haziness in the right maxillary sinus without a clear lateral wall of the sinus.

TREATMENT

The patient was treated with flucanazole 150 mg orally for 6 months, and a combination drug of cefoperazone and sulbactam 1.2 g intravenously for 10 days, both of which were given twice daily and metronidazole 100 ml intravenously thrice daily. Right maxillectomy was performed under general anaesthesia through Weber-Ferguson incision 4 days after starting the medication.

OUTCOME AND FOLLOW-UP

Maxillary wound healing was healthy, although large defects in the right maxilla persisted. The patient was asked to revisit every 10 days and later on once every month for 1 year during which he remained asymptomatic.

DISCUSSION

Platauf first explicated zygomycosis in his paper entitled 'Mycosis mucorina' in 1885. Mycologists prefer 'zygomycosis'

Figure 3 IOPA in relation to extracted 14, 15 and 16 revealed enlarged marrow spaces in the edentulous area. IOPA, intra oral periapical radiograph.

Figure 4 Occlusal radiograph revealed destruction of the anterior hard palate and maxillary alveolar process from 21 to 18.

and others use 'phycomycosis'. Since other members of this class can cause similar infection, clinicians preferably use 'mucormycosis'. The lay press has used terms like 'Black Death' and 'zombie disease' to describe this fungal infection but such terms can cause misunderstandings between the patients, their families and the public and thereby many clinicians opine to abandon these terms. In India, the frequency has scaled up from 13 cases per year in 1990–1999 to 36 cases per year in 2000–2004 and 50 cases per year in 2006–2007. Fungi belonging to the order Mucorales fall into Mucoraceae, Cunninghamellaceae, Mortierellaceae, Saksenaceae, Syncephalastraceae and Themidaceae families. Among these families Mucoraceae is the most frequent cause of mucormycosis. The chief species in order of frequency are *Rhizopus arrhizus* (*oryzae*), *Rhizopus microsporus* var. *rhizopodiformis*, *Rhizomucor pusillus*, *Cunninghamella bertholletiae*, *Apophysomyces elegans* and *Saksenaea vasiformis*. All cause similar disease in humans and even the diagnostic, treatment approaches are similar. These are ubiquitous saprophytes found on decaying vegetable matter, soil or as bread moulds. Spores are acquired by inhalation, ingestion or penetrating trauma. Germination is favoured by low oxygen, high glucose, acidic medium and high iron level which promote fungal growth by diminishing or inhibiting phagocytosis. Despite their continual exposure, they are not common infectious agents which are the evidence of their avirulence.

Figure 5 Branching, aseptate hyphae were demonstrated in H&E.

Figure 6 Multinucleated giant cells with Periodic acid-Schiff (PAS)-positive fragments in the cytoplasm demonstrated under PAS staining.

Immunocompetent individuals have strong natural immunity to the Mucorales by which the polymorphonuclear leucocytes can phagocytise the spores and kill the spores by generating oxidative metabolites and defensins (cationic peptides). If the spores escape phagocytosis, they can invade vessels, partly by efficacious adherence to endothelial cells, an ability that *R oryzae* maintains even when the fungus is not viable. *A elegans* has emerged as an important pathogen in immunocompetent individuals. In the immunocompromised, germination and hyphae formation occur and a variety of infections can develop including orbitorhinocerebral, pulmonary, gastrointestinal, cutaneous, renal and isolated central nervous system (CNS) infections. Risk factors in the development of mucormycosis include poorly controlled diabetes with or without ketoacidosis, long-term neutropaenia, chronic steroid use, metabolic acidosis, organ transplantation, leukaemia, lymphoma, iron overload and treatment with deferoxamine, AIDS, malnutrition and haematological malignancy.¹⁻⁴

The present case was suffering from uncontrolled diabetes since 20 years which is one of the common predisposing factors. Hyperglycaemia enhances fungal growth and impairs neutrophil chemotaxis. In a diabetic ketoacidotic patient there is a high incidence of mucormycosis caused by *R oryzae* also known as *R arrhizus* because they produce the enzyme ketoreductase which

Figure 7 Branching, aseptate hyphae were demonstrated under Grocott-Gomori's methenamine silver staining.

Figure 8 Hyphae invading the vessels demonstrated under Grocott-Gomori's methenamine silver staining.

allows them to utilise the patient's ketone bodies for their growth and proliferation.^{5,6} Mucormycosis is characterised by angioinvasion, thrombosis, infarction and necrosis of involved tissue and formation of gangrenous masses. Thereby it should be included in the differential diagnosis of maxillary necrosis in the immunocompromised as well as otherwise healthy patients. Fogarty *et al*⁷ reinforced the concept that simple procedures such as dental extractions can cause catastrophic complications in susceptible patients. In a review of 929 patients with mucormycosis, diabetes was the most frequent underlying condition (36%). The predominant clinical manifestations differ from host to host. Patients with diabetes most frequently present with rhino-orbital-cerebral manifestations (66%) followed by pulmonary (16%) and then cutaneous (10%) diseases, whereas patients with no underlying condition most frequently have cutaneous manifestations (50%). Patients receiving deferoxamine most frequently have pulmonary manifestations (28%). In injecting drug users, the order is cerebral (62%), cutaneous (11%) disease, and in solid-organ transplant recipients it is pulmonary (37–53%) and rhino-orbital-cerebral disease (31%).⁸

The rhino-orbital-cerebral form is the commonest form of mucormycosis which is usually silent, with unilateral facial swelling, headache, nasal or sinus congestion or pain, serosanguinous nasal discharge and sometimes fever. Only in advanced disease the symptoms are more specific with PNS, orbit or CNS involvement. Infections extending from the sinus to the oral cavity are limited to the hard palate and are generally ulcerative because of the necrosis caused by invasion of the palatal vessel. Necrotic black lesions on the hard palate or nasal turbinate and drainage of black pus from eyes, trigeminal or facial nerve palsy, ophthalmoplegia and loss of vision are useful diagnostic signs.⁵

Pulmonary mucormycosis generally occurs in patients with haematological malignancy or profound neutropaenia and in those who have been on steroid therapy. The symptoms include fever, cough, chest pain and dyspnoea. Angioinvasion results in necrosis of tissue which may ultimately lead to cavitation and/or haemoptysis. The reverse halo sign might be an early radiographic finding of pulmonary mucormycosis.⁹ Gastrointestinal mucormycosis is less common and is thought to arise from ingestion of the organism in patients who are severely malnourished and in transplant recipients. The stomach, colon and ileum are the most commonly involved sites. The symptoms are varied and depend on the site affected but non-specific abdominal pain and distention associated with nausea and vomiting are

the most common manifestations.¹⁰ Cutaneous mucormycosis may be primary or secondary. Primary infection is usually caused by direct inoculation of the fungus into disrupted skin and is most often seen in patients with burns or other forms of local skin trauma producing an acute inflammatory response with pus, abscess formation, tissue swelling and necrosis. The lesions may appear red, indurated and often progress to black eschars.¹¹ Secondary cutaneous infection is generally seen when the pathogen spreads haematogenously and the lesions typically begin as an erythematous, indurated and painful cellulitis and then progress to an ulcer covered with a black eschar. Disseminated mucormycosis may follow any of the four forms of mucormycosis described above but is usually seen in neutropenic patients with a pulmonary infection. The most common site of spread is the brain but metastatic necrotic lesions have also been found in the spleen, heart and other organs. Clinical manifestations include lethargy, changes in mental status or obtundation with or without a sudden onset of focal neurological signs.¹² Agents of the Mucorales may cause infection in virtually any body site. Brain involvement in the absence of sinus infection, endocarditis and pyelonephritis occur occasionally mainly in intravenous drug abusers. Other reports have described mucormycosis in bones, mediastinum, trachea, kidneys and peritoneum associated with dialysis. Other unusual forms of infection include superior vena cava syndrome and external otitis.

Presumptive diagnosis is based on the patient's history, physical examination and the patient's risk factors for getting a fungal infection. A definitive diagnosis is difficult. Although tests such as CT or MRI may help define the extent of infection or tissue destruction, their findings are not specific for mucormycosis. There are no serological or blood tests that is diagnostic for mucormycosis. Surgical removal of infected tissue and use of special tissue stains such as, Grocott methenamine silver stain, PAS staining, calcofluor white stain, immunofluorescence techniques can identify fungus from tissue debris as well help us make a definitive diagnosis. Hyphae are wide, non-septate and measure 10–20 µm in diameter, with branches which separate from the main body at almost 90°. Mucorales grow well on both non-selective and selective media. Growth is rapid with mycelial elements expanding to cover the entire plate in only a few days. The mycelium is described as fibrous or 'cotton candy-like' and its growth is so vigorous that the group has come to be known as 'lid lifters'. Identification of the agents responsible for mucormycosis is based on macroscopic and microscopic morphological criteria, carbohydrate assimilation and the maximum temperature compatible with its growth. Macroscopic criteria are helpful in establishing a presumptive identification, which should be confirmed by microscopic analysis after staining. Important macroscopic features are a hyaline appearance, vigorous growth, light colouration on the reverse side of the plate (tan to yellow for most species) and variable degrees of colouration on the sporulating surface of the colonies (from pure white to tan, brown, grey or even black). Species specification is microscopic and is based on the demonstration of important fungal elements such as rhizoids, stolons and columella visualised in the microbiology laboratory on lactophenol cotton blue-stained slides. The family Mucoraceae may be divided on the basis of the morphology of the predominant asexual spore producing structures namely sporangium producers, sporangia producers and merosporangium producers.¹³

Mucormycosis is considered to be a medical emergency. Early clinical recognition of this potentially fatal disease followed by aggressive debridement, systemic antifungal therapy and control

of underlying comorbid factors is the mainstay of therapy. Most patients will require both surgical and medical treatments. Two main goals are sought at the same time: antifungal medications to slow down or halt fungal spread and medications to treat any debilitating underlying diseases. Polyenes are the preferred therapeutic agents for mucormycosis. Amphotericin B, initially intravenous, is the usual drug of choice for antifungal treatment at higher than normal doses of up to 1.5 mg/kg/day. Renal functions are monitored to document amphotericin B-induced nephrotoxicity. Because poor vascular supply may prevent systemic therapy from reaching the fungus, local irrigation of infected tissues and medicinal packing of the areas allow higher doses to reach the site. Liposomal amphotericin B is recommended for persons with compromised renal function, those who are receiving other nephrotoxic therapies or those who are otherwise intolerant to amphotericin B. The advantages of lipid formulations of amphotericin B, particularly liposomal amphotericin B over amphotericin B deoxycholate in the treatment of mucormycosis may perhaps be due to better brain penetration, reduction of fungal burden, immunomodulatory effects and fewer nephrotoxic effects. The patients with underlying diseases like diabetes need to be optimally controlled. The patients normally on steroids are likely to have their medications stopped because they can increase the survival of fungi in the body.

Posaconazole, now used as an alternative to amphotericin B is a new, orally administered triazole antifungal and the first member of this class to have comparable *in vitro* activity to amphotericin B against most zygomycetes. It was usually given as an oral suspension of 200 mg four times a day or 400 mg twice a day. Fluconazole is also a triazole drug that interacts with 14- α -demethylase and cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Fluconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms, inhibit purine uptake and impair triglyceride and/or phospholipid biosynthesis. Fluconazole is primarily fungistatic; however, it may be fungicidal against certain organisms in a dose-dependent manner, specifically *Cryptococcus*. Exceptional results were obtained in the present case when fluconazole was used solely. There were case reports that describe successful outcomes with combinations of liposomal amphotericin B with either caspofungin or posaconazole, where single-agent therapy had failed. Adjunctive hyperbaric oxygen is another treatment modality that appears to be promising; oxygen in sufficient concentrations is fungicidal and decreases acidosis thereby increasing tissue survival. Interferon- γ and granulocyte-macrophage colony-stimulating factor have been shown experimentally to augment zygomycetes hyphal damage by polymorphs. The patients may need antifungal therapy for an extended time period of weeks to months depending on the severity of the disease.¹⁴

Surgical management also should be initiated early in the course of the treatment. This 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. Survival has improved dramatically, yet deaths still occur if the infection is not recognised and treated early in its course or if the source of immunocompromise is not reversible. Prognosis may improve with rapid diagnosis, early management and reversible underlying risk factors. The underlying disease is the most important determinant of survival. The complications of mucormycosis are serious and

are related to the body area initially infected, but also can occur in other body regions because the fungi often spreads to the organs or tissues that physically contact or are near the originally infected area. In addition, because surgical debridement is almost uniformly needed, some normal tissue may be destroyed because the surgeon must remove all the tissue that is dead or dying. Unfortunately, that means the surgeon may have to remove some normal tissue to insure all of the fungi are removed. For example, in the infection of the eye orbit; often the whole eye must be removed. Consequently, serious complications such as blindness, meningitis, brain abscesses, osteomyelitis, pulmonary haemorrhages, gastrointestinal haemorrhages, cavitory lesions in the organs and eventually secondary bacterial infections, sepsis and death may occur.

The overall survival rate of patients with mucormycosis is approximately 50%, although survival rates of up to 85% have been reported recently. Much of the variability in outcome is because of the various forms of the disease. Rhinocerebral mucormycosis has a higher survival rate than does pulmonary or disseminated mucormycosis because the rhinocerebral disease can frequently be diagnosed earlier and the most common underlying cause, diabetic ketoacidosis can be treated readily. In contrast, pulmonary mucormycosis has a high mortality because it is difficult to diagnose and it frequently occurs in neutropenic patients. Mortality in patients with disseminated disease approaches 100%, in large part because surgical removal of infected tissues is not feasible and in part because these patients tend to be the most highly immunocompromised.^{3 15}

Learning points

- ▶ Mucormycosis is a serious and life-threatening condition. Extra vigilance is crucial specifically in diabetic and other immunocompromised patients for early diagnosis, prevention of progression and successful treatment, thus reducing the mortality and morbidity rates.
- ▶ Atypical symptoms such as facial pain, sinus pain or unexpected odontalgia in otherwise healthy teeth should alert clinicians.
- ▶ Moreover, when a patient seems to deteriorate after dental therapeutic interventions, as in this case one should consider the possibility of rare lesions, such as mucormycosis, and promptly opt for meticulous intraoral examination and other investigations so as to reveal these non-conforming lesions.
- ▶ Novel regimens of combination therapies for the treatment of mucormycosis, that is, posaconazole along with a polyene, caspofungin, or both as well as empathetic use of triazoles have given away improved outcomes.
- ▶ Finally, prompt diagnosis, reversal of predisposing conditions and aggressive surgical debridement remain the cornerstone for therapies for this deadly disease.

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