Case Report

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A Rare Case of Pulmonary Mucormycosis Caused By Rhizopus Homothallicus in Post Heart Transplant Patient

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Abstract

We report a case of pneumonia due to Rhizopus homothallicus in a post cardiac transplant and diabetic patient. This is the rare case of R. homothallicus infection described in India and first case described in post cardiac transplant patient worldwide. The organism was isolated from broncho alveolar lavage fluid and identified after culture followed by amplification and sequencing of the internal transcribed spacer region

Keywords: *Rhizopus homothallicus*, Mucorales, Pneumonia

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Introduction

Mucorales are ubiquitous fungi causing infection in immunocompromized hosts like carcinomas, immunosuppressive therapy, uncontrolled diabetes, neutropenia, or patients on desferroxamine therapy amongst which pulmonary mucormycosis is the second common [1]. Mucormycosis is characterized by host tissue infarction and necrosis resulting from vasculature invasion by hyphae starting with a specific interaction with endothelial cells [2]. However, infections due to *Rhizopus homothallicus* appear to be rare compared with those caused by other species of *zygomycetes* [3]. Low incidence may be attributed to reduced pathogenicity or its lower prevalence in the soil compared with other *Mucor* species.

Case Report

A 57-year-old male, known case of post cardiac transplant 5 years back (on triple-drug immunosuppression -cyclosporine, azathioprine, and prednisolone) along with type II diabetes mellitus for more than 13 years with diabetic triopathy, hypertension, non-oliguriac end stage renal disease (stage IV) presented to us with high grade fever with cough, generalized weakness and loss of appetite of one week duration. He had history of hospitalization around two months back for acute gastroenteritis. He was on antihypertensive drugs (β-blockers, calcium channel blocker and alpha blocker) and insulin for diabetes mellitus. His chest X-ray revealed focal patch of opacity in right mid-lower zone suggestive of consolidation. At our institute, contrast-enhanced computed tomography of the thorax revealed patchy sub-lobar consolidation in right middle and lower lobes with surrounding ground glass attenuation with large inhomogeneous area of ground glass attenation in right perihilar region with small mediastinal and right hilar lymphadenopathy suggesting possibility of mycoytic pathology (**Figure 1**). No pleural effusion was noticed. Echocardiography ruled out endocarditis. His blood sugar levels ranged from 153 to 226 mg/dl, total leucocyte counts 14600 per cumm with polymorphs 84%, B. urea 103, S. Creatinine 4.1. His serum procalcitonin levels were raised along with HbA1c of 12.82, indicating uncontrolled diabetic status.

Diagnostic bronchoscopy was performed and direct microscopic examination with 10% KOH of the bronchoalveolar lavage specimen revealed ribbon-like broad aseptate hyphae with branching at right angles. The samples were cultured on Sabouraud's dextrose agar (SDA) (HiMedia, Mumbai, India) and

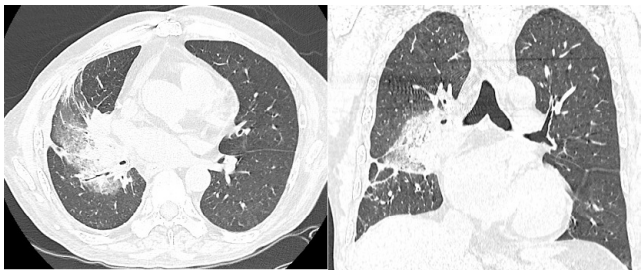

Figure 1 CT Chest lung window- sub-lobar consolidation involving right middle and lower lobes with surrounding ground glass haziness.

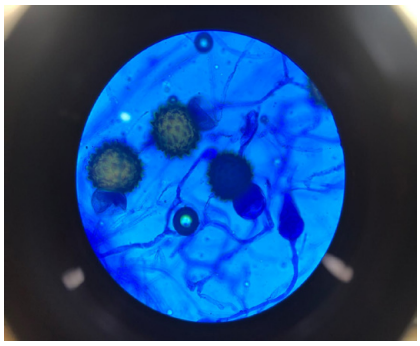

Figure 2 Lactophenol cotton blue mount of *R. homothallicus* showing golden brown, globose zygospores with stellate spines.

incubated at 25° and 37°C. After 4 days of incubation, fast growing, cottony, white colonies were obverse with no pigmentation on the reverse side of the tubes. The colonies turned grey after prolonged incubation for 10 days. The colonies were teased and stained with lactophenol cotton blue. When studied under microscope, it showed poorly developed rhizoid tufts from which arose few lateral sporangiophores measuring 100–150 µm in length. These bore a few globose sporangia with scanty globose sporangiospores. A few globose, hyaline, intercalary chlamydospores were also present. Sequential microscopic changes could be observed as a large number of dark brown zygospores measuring 60–100 µm in diameter with stellate spines on their walls which developed after prolong incubation. The suspensor cells were uneven with the zygospores attached to the larger, globose suspensor cell (**Figure 2**). The isolates were thermotolerant and were able to grow when incubated up to 48 °C. Based on these characteristics, the isolates was presumptively identified as *Rhizopus homothallicus.* The isolate was further confirmed by nucleotide sequencing of the 28S ribosomal RNA (rRNA) region. The basic local alignment search tool (BLAST) was used to compare the sequences obtained with those in the GenBank database and to see the similarity of the isolate. The sequences of isolate gave 98% identity with the ex-type strain of R. homothallicus (CBS 336.62; GenBank: KU926333.1).

The patient was initially treated with broad spectrum antibiotics along with antifungal voriconazole and echinocandins which was later changed to intravenous liposomal amphotericin B 3-5 mg/kg IV qDay for 10 days. After a cumulative dose of 750 mg of amphotericin B, thepatient developed acute renal failure and was managed with hemodialysis at regular intervals. After showing initial improvement on amphotericin B, deteriorated subsequently and developed sepsis leading to multi-organ failure and death.

Discussion

Among the agents of zygomycosis, Rhizopus spp. are the most commonly implicated agents causing human infection. This is followed by genera such as Lichtheimia and Mucor. Among Rhizopus spp., R. *oryzae* is the predominant species, being implicated in 90% of the reported cases of invasive zygomycosis [3] *R. homothallicus* which was earlier considered an environmental isolate, has been increasingly reported to cause invasive infections. It has been reported to cause invasive pulmonary mucormycosis, rhino-orbitocerebral and cutaneous mucormycosisin six patients in India [4-6]. One case of fatal invasive pulmonary mucormycosis has also been reported from France [7].

Mucorales gain entry to a susceptible host through inhalation, ingestion of contaminated food, or through abraded skin. One of the characteristic features of mucormycosis is its angioinvasive property, resulting in vascular thromboses and ultimately tissue necrosis. Angioinvasion was reported to be related to the interaction between a spore-coating protein family (CotH) on *Rhizopus* spp. surface and endothelium glucose regulator protein 78 (GRP78) expressed at the surface of endothelial cells. This interaction triggers host cell injury and subsequent fungus hematogenous dissemination [8]. Elevated levels of serum glucose, iron, and ketone bodies increase fungal growth and induce the expression of GRP78 and CotH, resulting in increased ability of *Rhizopus* to invade host tissues and explaining the susceptibility of diabetic and deferoxamine treated patients to mucormycosis [8].

In India, Chakrabarti et al. have described an overall prevalence of rhino-orbito-cerebral mucormycosis (48%), followed by pulmonary mucormycosis (17%), gastrointestinal mucormycosis (13%), cutaneous mucormycosis (11%), renal and disseminated mucormycosis (5% each) [4]. The MIC patterns observed with the isolates of *R. homothallicus* were consistent with those reported for other *Rhizopus* species with amphotericin B MIC of 0.5 µg/ml [4]. This suggests that the first-line recommended antifungal agent is liposomal Amb (L-Amb) or Amb lipid complex (ABLC). ECMM/ESCMIDand ECIL-6 guidelines recommend the use of L-Amb with a daily dosage of at least 5 mg/kg/day for mucormycosis [9,10]. Recently, isavuconazole has been added to the armamentarium of antifungal agents, however, its use has not yet been specified in the most recent guidelines [9]. Management of Invasive mucormycosis includes comprehensive approach like antifungal therapy, surgery and control of underlying conditions like reduction of immunosuppressive therapy in this case.

Conclusion

The purpose of this case report is to emphasise that R. homothallicus, although a rare fungus, its differentiation is important as it has major therapeutic implications. Mucormycosis

is a life-threatening fungal infection causing angioinvasion that occurs mostly in immune-compromised patients and is associated with an increasing incidence and mortality despite the availability of therapeutic tools. Earlier diagnosis and optimal medico-surgical treatment can improve survival and reduce morbidity. Comparative studies are needed to better optimize induction and consolidation treatment.

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