Case Report

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Breakthrough mucormycosis after voriconazole use in a case of invasive fungal rhinosinusitis due to *Curvularia lunata*

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Summary **Invasive fungal rhinosinusitis (FRS) is a potentially fatal illness requiring early diagnosis and aggressive treatment with surgery and antifungals. We report a case of chronic FRS in a recently diagnosed diabetic individual due to *Curvularia lunata*. Imaging revealed extension into the right orbit and right basifrontal lobe. This was further complicated by development of nosocomial mucormycosis which was attributed to voriconazole therapy. The patient responded well to debridement and amphotericin B based therapy. To our knowledge, there are no reported cases of invasive FRS due to *Curvularia lunata*. Also, breakthrough mucormycosis on voriconazole therapy is rarely seen in non-malignancy, non-transplant settings. The possibility of rare fungal infections (community and nosocomial) should be entertained in developing settings where fungal spores are ubiquitous.**

Keywords: Phaeohyphomycetes, Sino-orbital cerebral

1. Introduction

Rhinosinusitis is the inflammation of mucus membrane of nose and paranasal sinuses causing obstruction of the opening of the sinuses. Rhinosinusitis due to fungi can either be caused by the direct invasion of fungus into the nasal and paranasal sinus tissues or by allergic inflammatory response of the host to the fungus. The invasive fungal rhinosinusitis (FRS) can be further divided into acute (< 4 weeks) or chronic (> 12 weeks). Acute invasive FRS is a rapidly progressive infection of the immunocompromised host which commonly extends to involve orbit and brain. Mucormycetes and *Aspergillus* spp. are commonly implicated in acute FRS. Chronic FRS, on the other hand has a slow and indolent course and is usually limited to the sinuses and orbit and does not involve the brain. The common fungi implicated in chronic FRS is *Aspergillus* spp. Fungal rhinosinusitis is commonly reported from the Asian countries, more so from the Indian subcontinent. Invasive fungal sinusitis, particularly acute FRS, are potentially fatal, if not identified early and treated with aggressive surgery and systemic antifungals. We report an unusual case of chronic invasive FRS caused by *Curvularia lunata* which got complicated by development of superimposed acute invasive FRS due to mucormycosis.

2. Case Report

A 55 years old gentleman, known hypertensive (controlled) on irregular medication (Tablet amlodipine) presented with fever for three and half months, headache for three months and loss of vision in the right eye for one and half month. He was apparently asymptomatic three and half months back, when he started having continuous fever with evening rise in temperature and cough with mild expectoration. There was no associated history of breathlessness, haemoptysis, loss of appetite or loss of weight. Two weeks into the illness, patient started having right sided intermittent headache associated with redness and watering of right eye with right peri-orbital swelling. The patient was prescribed topical and oral antibiotics after which the eye symptoms resolved partially but the fever and headache persisted. Two months into the illness, he had sudden

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painless loss of complete vision in the right eye. On general examination, his core body temperature was 101 Fahrenheit, pulse was 110/minute and blood pressure was 150/94 mm of mercury. On ophthalmological examination, he had ptosis in the right eye and loss of perception of light in the right eye. The right optical disc showed complete pallor and optic atrophy. There was mild tenderness over the frontal and maxillary sinus. Rest of the general and systemic examination was normal. On initial laboratory investigations, haemogram, liver function tests and kidney function tests were within normal limits. His HbA1c was found to be 6.9%. Enzyme linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) 1 and 2 was non-reactive. Chest X-ray showed areas of consolidation with air bronchogram in right upper and middle zone suggestive of active infection. The patient was started on empirical anti-tubercular therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Magnetic resonance imaging (MRI) of the brain, orbits and paranasal sinus revealed extensive sinusitis involving the bilateral maxillary, ethmoidal and frontal sinus with extension into the right orbit (sub periosteal abscess) and right basifrontal lobe in form of multiple ring enhancing lesions with perilesional oedema (Figure 1). The patient was started on intravenous amphotericin B with a suspicion of invasive fungal infection. Biopsy from the right maxillary sinus showed septate hyphae with acute angle branching on potassium hydroxide (KOH) mount (Figure 2). There was no granulomatous reaction on histopathology. The biopsy sample was inoculated in three tubes containing Sabourad dextrose agar (SDA), SDA with gentamycin and SDA with gentamycin and cycloheximide. All the three tubes were incubated at 37 degrees celsius. Four days after inoculation, a black mould was seen to be growing on the obverse with dark pigmentation on the reverse in the tube with SDA containing gentamycin and cycloheximide. The dematiaceous fungi was identified as *Curvularia lunata* based on the micro-morphological features (Figure 3). With a provisional diagnosis of cerebral phaeohyphomycosis, voriconazole was added to the existing regimen of amphotericin B. The contrast enhanced computed axial tomography (CECT) Chest showed areas of consolidation with ground glass opacities, multiple cavities and centrilobular nodules with tree in bud appearance. The features were consistent with both pulmonary tuberculosis and aspergillosis. Meanwhile, a broncho-alveolar lavage (BAL) was planned to confirm the diagnosis of tuberculosis. The BAL from the right upper lobe was positive for gene Xpert

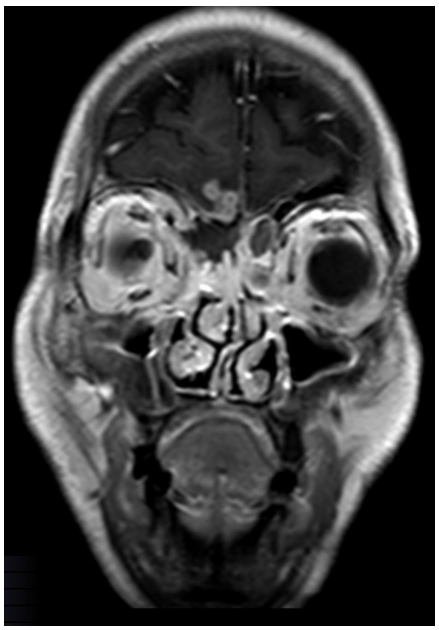

Figure 1. CEMRI showing extensive sinusitis involving the bilateral maxillary, ethmoidal and frontal sinus with extension into the right orbit (sub periosteal abscess) andextension into right basifrontal lobe in form of multiple ring enhancing lesions with perilesional oedema.

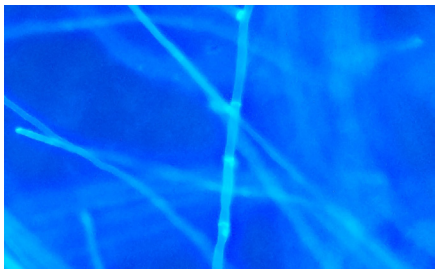

Figure 2. Biopsy from the right maxillary sinus showed septate hyphae with acute angle branching on Calcofluor-KOH mount.

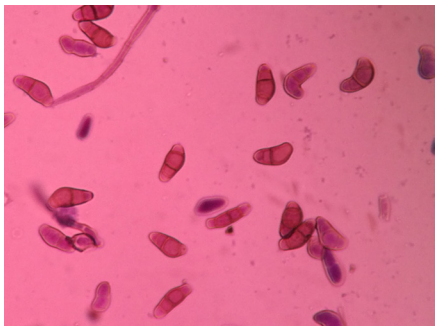

Figure 3. Lacto phenol cotton blue mount made from the growth on SDA tube shows micromorphological features suggestive of *Curvularia lunata*.

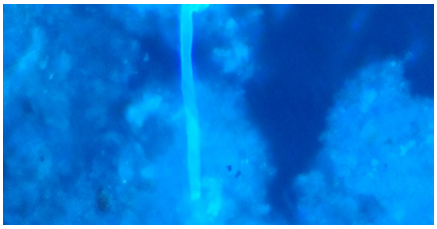

Figure 4. Calcuofluor KOH mount from the emergency debridement showed broad aseptate hyphae suggestive of invasive mucormycosis.

(cartridge based nucleic acid amplification test). Direct KOH mount and fungal culture were negative for BAL. Both serum and BAL galactomannan antigen (OD: – 0.7 and 1.54, respectively) were positive. Since *Curvularia lunata* does not give a positive galactomannan and is rarely associated with the current clinical scenario, it was considered as a contaminant. The diagnosis was revised to sino-orbital cerebral aspergillosis with possible pulmonary aspergillosis and tuberculosis with type II diabetes mellitus. In the hospital course, he showed improvement with respect to fever and headache and was planned for discharge on oral voriconazole. Therefore, his amphotericin was stopped after he had received 16 days of intravenous amphotericin B and 7 days of intravenous voriconazole therapy. After three days of isolated voriconazole therapy, he developed fever, swelling in the right eye and headache. With a suspicion of acute invasive FRS, emergency debridement was planned where the unhealthy hypertrophic mucosa from the maxillary sinus was removed. The KOH mount showed broad aseptate hyphae suggestive of invasive mucormycosis (Figure 4). Fungal cultures were negative. Voriconazole was immediately stopped and the patient was again started on intravenous amphotericin B. After initiation of amphotericin B, the symptoms improved again. The patient received 25 more days of intravenous amphotericin B after which a repeat MRI was done which showed partial resolution in the sinus and orbital lesions. The vision loss and partial ptosis, however did not improve. An ophthalmological consultation was sought and the vision loss and partial ptosis was attributed to optic nerve and oculomotor nerve involvement secondary to invasive fungal infection. None of the samples were positive for fungal culture except the previous sample which showed growth of *Curvularia lunata* in one of the tubes. Pan fungal polymerase chain reaction (PCR) assay was positive for both the samples but primers specific for mucormycetes was positive only in the second sample suggestive of acquisition of mucormycosis during the voriconazole therapy (*1*). Aspergillosis specific primers were however, negative for both the samples (*2*). Considering the stable status of the patient, he was discharged on oral posaconazole therapy. The patient was maintained well on anti-tubercular therapy and posaconazole on follow-up after three months of discharge.

3. Discussion

Chronic invasive FRS is commonly reported from patients who are mildly immunocompromised like the ones with diabetes mellitus or those who are on long term steroids. Our patient was diagnosed with type 2 diabetes mellitus at the time of admission based on his persistently elevated sugar levels and HbA1c reports. The patient was empirically started on broad spectrum amphotericin B at presentation. The initial biopsy showed septate hyphae which was later proven to be *Curvularia lunata*. Although, there has been some reports of *Curvularia lunata* being a cause of allergic FRS and cerebral abscess, there are no reports of it being associated with chronic invasive FRS (*3-6*). The treatment for infections due to *Curvularia lunata* are not standardized but most retrospective studies show a combination of amphotericin B and triazole to be the best choice (*7*). Therefore, voriconazole was added to our patient in addition to amphotericin B.

Sino-orbital-cerebral aspergillosis is a specific entity described mainly from the Indian sub-continent. It usually manifests with extra-ocular palsies and features of mass lesion in the brain. Imaging usually shows masses within the paranasal sinuses with extension into the orbit and cranial fossae (*8*). Owing to the positive galactomannan and the known fact that Aspergillus spp. is the most commonly implicated pathogen in chronic invasive FRS (*6,9*), the diagnosis was further revised. But, after the molecular results were available, in hindsight, the patient was likely to be suffering from *Curvularia lunata* infection and not invasive aspergillosis. The initial biopsy sample was positive by pan fungal PCR but negative when Aspergillus spp. specific primers were used. Also, the positive galactomannan could have been explained by the piperacillin-tazobactam, the patient was receiving at that time.

The patient showed resurgence in symptoms during the hospital stay. This debridement sample was positive by microscopy and PCR assay for mucormycetes. The diagnosis of newly acquired mucormycosis was based on the fact that in comparison to the second sample, the first sample was negative for mucormycetes by both microscopic and molecular methods. Though mucormycosis is commonly known as a community-acquired disease, nosocomial infections have been reported in recent years (*10*). The risk factors that would have increased the susceptibility of our patient to mucormycosis were voriconazole use, pre-existing sinusitis and diabetes mellitus. Voriconazole exposure is known to cause breakthrough infection with mucormycetes. It has been noted in experimental fly and mouse models that mucoraceous fungi become more virulent after voriconazole exposure (*11*). Most cases of mucormycosis in patients receiving voriconazole has been reported in transplant recipients and patients with haematological malignancy (*12*). Ours was a rare case of breakthrough mucormycosis in an individual who was otherwise immunocompetent, except for his diabetes.

It is imperative to understand, in the age where diabetes is so common, and in settings where fungal spore burden is very high, rare species will cause more and more disease. Also, in patients with risk factors for mucormycosis, even as rare as voriconazole use, intensive monitoring should be a rule, considering high mortality associated with the disease. The patient could

be saved from a potentially rare and intractable disease because of early suspicion, quick diagnosis and prompt initiation of treatment.

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