Case Report

Refractory bronchovascular pleuropulmonary mucormycosis: Case report and difficulties in management

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ABSTRACT

Pulmonary mucormycosis is a life-threatening opportunistic fungal infection. It is considered as a disease of immunocompromised state and is rarely seen in immunocompetent patients. We here report a case of refractory bronchovascular pleuropulmonary mucormycosis, who despite early detection, optimal management with liposomal amphotericin B, and posaconazole therapy followed by surgery, progressed further and led to a fatal outcome. Dual antifungal therapy combined with surgery is the only definitive treatment option available in the literature. Many new therapeutic options for mucormycosis treatment have become available but none have shown promising results, and larger studies are required to assess their efficacy.

KEY WORDS: Antifungal therapy, disseminated mucormycosis, opportunistic fungal infection, pleuropulmonary mucormycosis

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INTRODUCTION

Disseminated mucormycosis has been reported to be refractory to medical as well as surgical treatment in immunocompromised patients with underlying hematological malignancies.[1] Although serious mucormycosis develops in nonmalignant immunocompromised host secondary to diabetes, mostly it is localized and amenable to medical and surgical therapy with early diagnosis.[2] We here report a case of disseminated, progressive mucormycosis with the involvement of bronchus, lung parenchyma, and pleura in a diabetic male which became refractory to medical therapy with liposomal amphotericin B and posaconazole and underwent pleuropneumonectomy. Postoperatively, dual antifungal therapy was further strengthened by adding micafungin, but due to vascular and mediastinal invasion, patient could not be saved and succumbed to fulminant therapy-resistant mucormycosis.

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CASE REPORT

A 62-year-old male, nonsmoker, and diabetic for 20 years, presented with complaints of dry cough and fever with chills for the past 20 days. Patient had a history of hemoptysis (3–4 episodes) 2 days prior with no other significant past histories. He received empirical antibiotics in the peripheral hospital with no clinical response. Physical examination showed heart rate - 102/min, blood pressure - 160/90 mmHg, respiratory rate - 18/min, SpO_2 = 93% on room air, and diminished right-sided breath sounds on chest auscultation. On blood investigations, hemoglobin was 11.6 g/dl, total leukocyte count 11300/mm^3, platelet count 3.90 k/uL, and glycated hemoglobin – 9.8%, with normal kidney and liver functions tests. Chest X-ray revealed right parahilar opacity [Figure 1a] and contrast-enhanced computed tomography chest showed right hilar mass

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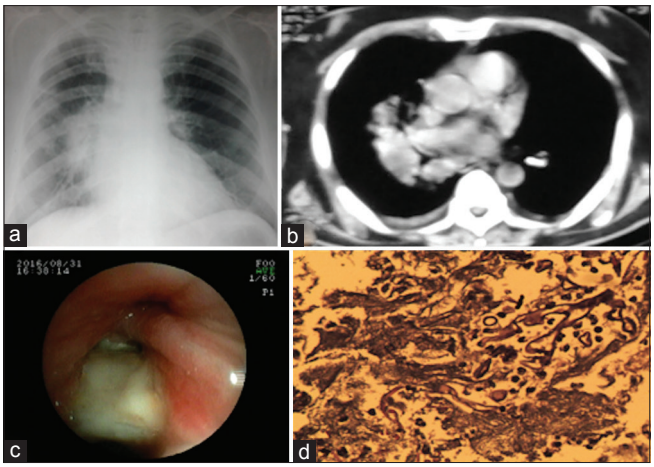

Figure 1: (a) X-ray chest showing right parahilar opacity, (b) contrast-enhanced computer tomography chest showing right hilar mass compressing intermediate bronchus, (c) fiber-optic bronchoscopy showing thick whitish necrotic material filling right intermediate and lower lobe bronchi, (d) bronchial biopsy showing aseptate acutely branching hyphae suggestive of mucormycosis

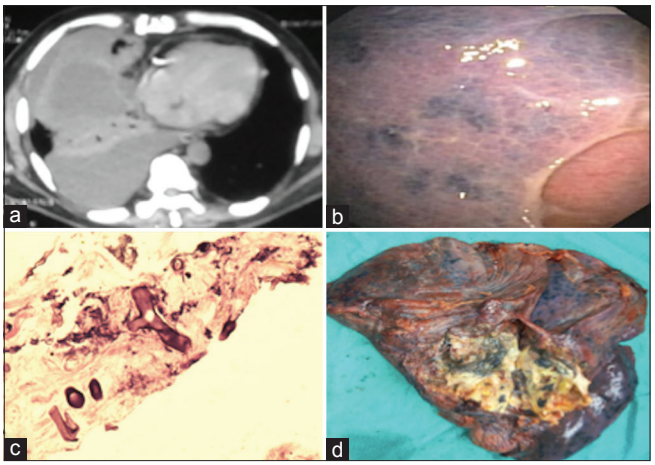

Figure 2: (a) Repeat computer tomography chest showing collapse consolidation of right lower lobe with right-sided moderate pleural effusion, (b) medical thoracoscopy image showing thick pleura over both parietal and visceral surfaces with blackish deposits, (c) biopsy of parietal pleura showing fungal invasion by Mucorales, (d) pneumonectomy specimen showing extensive necrosis with Mucorales

compressing intermediate bronchus [Figure 1b]. Immediately, postadmission patient had massive hemoptysis and was transferred to respiratory intensive care for stabilization, following which fiber-optic bronchoscopy was done revealing thick whitish necrotic material filling right intermediate and lower lobe bronchi [Figure 1c]. Bronchial lavage was negative for acid-fast bacilli and pyogenic cultures were sterile. Bronchial biopsy confirmed aseptate acutely branching hyphae suggestive of mucormycosis [Figure 1d]. Fungal culture showed no growth after 3 weeks.

Patient was started on liposomal amphotericin B at a dose of 3 mg/kg daily and increased to 5 mg/kg daily along with intensive blood sugar control with insulin. However, he continued to have high-grade fever with chills and repeat CT chest revealed collapse consolidation of right lower lobe with right-sided moderate pleural effusion [Figure 2a]. Diagnostic pleural fluid analysis was suggestive of exudative neutrophilic effusion with low adenosine deaminase. Medical thoracoscopy was performed which showed thickened pleura with blackish deposits over both parietal and visceral surfaces. Biopsy of parietal pleura demonstrated fungal invasion by Mucorales [Figure 2b and c]. In view of progression, dose of amphotericin B was escalated to 7.5 mg/kg/day and oral posaconazole (400 mg twice daily) was added. Despite this, patient continued to deteriorate clinically and radiologically, with accumulation of more pleural fluid with loculations. In view of rapid progression despite on dual antifungal therapy, the patient was taken up for decortication with lobectomy/pneumonectomy as a high-risk case. Perioprative, there was extensive invasion of pulmonary vessels and pericardium requiring removal of affected pericardium with *en bloc* pneumonectomy and parietal pleurectomy. Immediate postoperative period was uneventful, but patient continued to have fever. Pneumonectomy specimen showed extensive necrosis with nonseptated hyphae [Figure 2d], and third antifungal micafungin was also added. Despite three antifungals and surgical excision, patient continued to worsen and died 10 days postoperatively.

DISCUSSION

Fungi from Mucorales order typically cause acute, aggressive, and angioinvasive infections in immunosuppressed hosts, which is most lethal of all fungal infections. The treatment strategies in such patients though varied have variable positive results. In nonmalignant immunocompromised patients, for example, uncontrolled diabetes and long-term steroids use, mucormycosis is considered to be amenable to antifungal and surgical treatment. Case reports have shown cure even without using amphotericin B in localized disease without angioinvasion.[3] However, our case had extensive and disseminated disease involving bronchus, lung parenchyma, and pleura, with progressive invasion of mediastinal structures and pericardium. Endobronchial mucormycosis is shown to be more common in diabetic patients;[4] in a review of 87 cases, 85% of patients having endobronchial mucormycosis were found to have underlying diabetes mellitus.[5]

The overall mortality of pulmonary mucormycosis is approximately 50%–70% but is >95% if it is disseminated.[6] High mortality in this disease is multifactorial. Delay in diagnosis due to: (1) physicians unawareness about disease, especially in not so high-risk group, for example, uncontrolled diabetes mellitus or prolonged corticosteroid use, (2) low sensitivity of sputum and bronchoalveolar lavage fungal cultures, (3) requirement of histopathological demonstration of fungi in lung biopsy for diagnosis, and (4) molecular methods not yet available freely for early and accurate diagnosis.[7] In our case, high index of suspicion on account of clinical and radiological findings with early biopsy demonstrating

Mucorales led to early initiation of appropriate antifungal amphotericin B.

Liposomal amphotericin B is the drug of choice for the management of mucormycosis but has been shown to achieve low drug levels in pleural fluid.[8] Hence, chest drainage by intercostal tube is recommended as an adjunct for cases with pleural involvement as was done in our case. Amphotericin B resistance in Mucorales is being reported increasingly, particularly in species other than Rhizopus[9] and need for another antifungal drug to increase the efficacy of medical therapy was felt worldwide. Fluconazole and voriconazole do not have reliable activity against Mucorales. A retrospective study on posaconazole showed a complete response in 64.6% of 42 patients with overall mortality of 24%.[10] Dual therapy with amphotericin B and posaconazole has been tried as salvage therapy in case reports as mortality with amphotericin B monotherapy is unacceptably high. Iron metabolism plays a central role in regulating mucormycosis infections. Deferoxamine predisposes patients to mucormycosis by inappropriately supplying the fungus with iron; hence, possible role of iron chelator therapy in Mucorales management has been suggested.[11] Recent data give options of combination therapy using lipid-based amphotericin B with an echinocandin or with a posaconazole or with all three as triple therapy.[12] We tried this triple therapy by adding micafungin to amphotericin B and posaconazole with no clinical benefit.

Successful treatment of bronchovascular mucormycosis with invasion of superior vena cava by surgical management has been reported.[4] However, in our case, lung parenchyma, pleura, pericardium as well as right pulmonary artery was associated with invasive mucormycosis indicating much more extensive disease. Experimental therapies with iron chelating agents or granulocyte macrophage colony-stimulating factor have been used in anecdotal case reports, but we did not use these choices over more conventionally used treatments. Isavuconazole showed activity against mucormycosis with efficacy similar to amphotericin B, in a single-arm open-label trial (VITAL study).[13]

This case highlights the urgent need for further research in treatment of extensive mucormycosis. At present, it has been emphasized that early diagnosis is main determinant of survival in this life-threatening and increasingly recognized entity in uncontrolled diabetics. Our case showed that despite early diagnosis and management as per guidelines, outcome is poor in extensive mucormycosis. Although salvage therapies tried in our case did not work, more Phase III trials are needed to address such issues as raised by our patient.

CONCLUSION

Disseminated mucormycosis is a rare presentation in diabetic patients. Early diagnosis is key to the successful management in most of the cases. Some cases may be refractory to treatments, in which double or triple combination of antifungal drugs should be tried along with surgical management. Despite therapy, outcome is poor in extensive disease.

Limited evidence is available for newer drugs in the treatment of mucormycosis, and further research for the same is the need of hour.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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