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A Rare Case of Pulmonary Mucormycosis Successfully Treated with Dual Antifungal Agents and Surgery in a Patient with Uncontrolled Diabetes

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Abstract

Pulmonary mucormycosis is an emergent and life-threatening invasive fungal infection underdiagnosed by clinicians due to unspecific clinical picture and lack of awareness. Although the acknowledgment of risk factors, clinical and radiological findings may increase early recognition, the definite diagnosis is challenging to establish and the ideal treatment has never been delineated. The authors describe a rare case of pulmonary mucormycosis that was successfully treated with dual antifungal treatment and surgery in a patient with uncontrolled diabetes. When last evaluated, he was asymptomatic with no evidence of relapse. To our knowledge this is a rare report of a successfully treated diabetic patient with pulmonary mucormycosis with L-AmB, triazole posaconazole and surgery with no evidence of recurrence. We highlight the importance of clinicians' awareness to early diagnosis, combined antifungal treatment and adjuvant surgery as the greatest chance of cure of a rapidly progressive disease with high mortality and morbidity.

Keywords

Pulmonary Mucormycosis, Diabetes, High Mortality

1. Introduction

Mucormycosis is an unusual and life-threatening opportunistic fungal infection, caused by environmental nonseptate molds dispersed in soil, plants and decomposing materials of the class *Zygomycetes*. Most frequently, the

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order *Mucorales* [1]. *Mucor*, *Absia* and *Rhizopus* are the most regularly seen genera [2]. Mucormycosis is categorized attending to the site of infection, being rhino-orbital-cerebral infection, followed by pulmonary involvement, the most common syndromes. Pulmonary mucormycosis accounts for more than 30% of all the reported cases [1] [3] and exposure occurs by inhaling aerosolized mucor spores from the environment.

A high index of suspicion, mostly in predisposed populations, is primordial in the management of this invasive and potentially fatal fungal infection. It is reported mainly in patients with diabetes, immunosuppressive therapy, neutropenia, hematologic malignancies, organ transplant recipients and trauma [3]-[5]. Prevalence of mucormycocis infections is increasing due to the expanding of diabetes, cancer and transplantation in aging populations in developed countries. The incidence is problematic to define due to the minor number of studies on this entity. The prognosis for mucormycosis is improved in diabetic patients than for hematological malignancies [5].

Early diagnosis as prompt therapeutic intervention is imperative. Commonly, thrombosis of pulmonary vessels due to fungal angioinvasion of lung parenchyma and airways associated to pulmonary parenchymal progressive necrosis may occur [6]. Disseminated mucormycosis is also a possible clinical picture. Due to the relative rarity of this entity, prospective and comparative studies of therapeutic strategies are lacking. Here we present a case of a successfully treated invasive pulmonary mucormycosis in a 70-year-old man previously diagnosed with diabetes mellitus.

2. Case Report

A 70-year old man with a previous history of uncontrolled type 2 diabetes mellitus of 15 years duration, presented with a one-day history of fever and a 2-week history of scarce productive cough with purulent sputum. In the review of organs and systems, patient had no other significant comorbidities. No history of known respiratory disease, recent travel, substantial smoking or intravenous drug use. Residence had good hygiene without pets. No significant epidemiological context.

The patient was afebrile with a heart rate of 75 beats per minute, blood pressure of 167/79 mmHg and a respiratory rate of 28 breaths per minute. Oxygen saturation was 96% on room air. The remainder of the patient's physical examination was unremarkable. Laboratory analysis showed leukocytosis (14.21 × 10^9/L [4.0 - 11.0 × 10^9/L]) with neutrophilia (9.6 × 10^9/L [1.9 - 7.5 × 10^9/L]) and elevated C-reactive protein (26.2 mg/dL [<0.5 mg/dL]); elevated urea (80 mg/dl [10.0 - 50.0 mg/dL]) and creatinine (1.6 mg/dl [0.7 - 1.3 mg/dL]). Glucose of 600 mg/dL [70.0 - 100.0 mg/dL], hemoglobin A1C was 12.3% [<5.7%] and arterial serum pH was 7.325 [7.35 - 7.45]. Liver function tests, coagulation, and remainder chemistry were normal. Summary analysis of urine showed glycosuria (1000 mg/dL) and evidence of ketones without parameters suggestive of infection. A chest x-ray revealed as mall opacity in the left upper lobe (**Figure 1(a)**). With a diagnosis of suspected community acquired pneumonia, empiric treatment with amoxicillin-clavulanate (1.2 mg every 8 hours) intravenously was initiated. During hospitalization, the patient remained afebrile, hemodynamically stable with oxygen saturation superior to 94% on room air. Clinically, it was verified improvement of productive cough, with periods of irritating dry cough associated with progressive installation of asthenia, without other identifiable symptoms. It was accompanied by persistently elevated inflammatory parameters and progressive glycemic control. Blood cultures (bacteriological examination aerobically and anaerobically) and urine cultures were negative.

Patient was empirically medicated with multiple cycles of intravenous antibiotics adjusted to renal function, including amoxicillin/clavulanic acid (1.2 mg every 8 hours during 7 days), levofloxacin (750 mg every 48 h) associated with metronidazol (500 mg every 8 hours) during 10 days and piperacillin/tazobactam (2.25 mg every 6 hours for 18 days). A revaluation chest X-ray after antibiotics revealed an extensive opacification involving the left upper lobe along with multiple air levels (**Figure 1(b)**). Computed tomography (CT) of the chest revealed a lesion with a 5 cm larger diameter within the left upper lobe, with low attenuation center suggestive of necrosis and some air levels; that injury involved the left upper lobe bronchus, with close contact with the left pulmonary artery in accordance with the hypothesis of a neoplasic lesion; and some "ground glass" densification and interlobular septal thickening adjacent to the lesion described (**Figure 2 (a)**). Tumor markers (CEA, CA 125, CA 19 - 9, CYFRA21-1 and NSE) were within the normal range. Aspergillus serologies, including galactomannan, and human immunodeficiency virus (HIV) serology were negative.

Flexible bronchoscopy (FB) revealed a marked decrease in the diameter of the left lung bronchus by extrinsic compression and macroscopic appearance suggestive of fun galetiology. The bronchoalveolar lavage (BAL) and

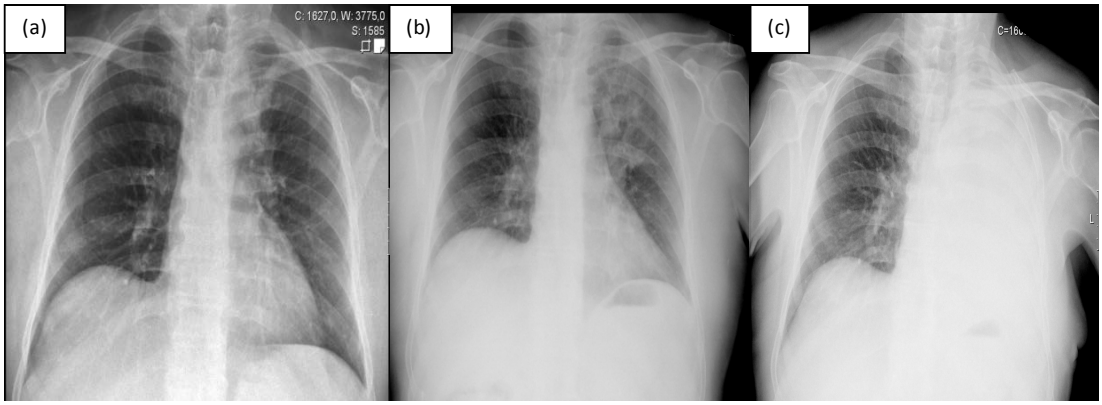

Figure 1. (a), (b) and (c) Chest radiograph (a) and (b) revealing a small opacity in the left upper lobe that progressed to an extensive opacification with multiple air levels, previously to surgery. Chest radiograph (c) after surgery.

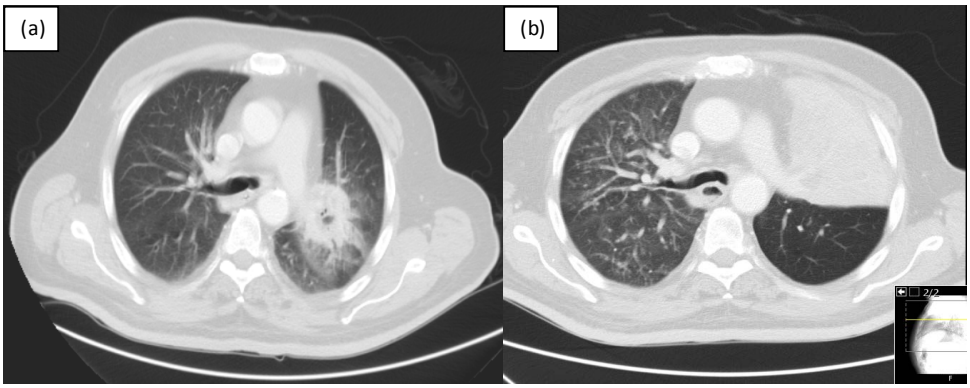

Figure 2. (a) and (b) CT of the chest revealing a lesion with a necrotic center in the left upper lobe, previously to surgery and CT of the chest after surgery.

transbronchial biopsies (TBB) revealed *Pseudomonas aeruginosa* sensitive to amikacin and piperacillin/tazobactam; bronchial mucosa fragments with marked lymphocytic inflammatory infiltrate and a necrotic fragment with numerous fungal nonseptatedhyphae. The organism was provisionally identified as *Mucor* on the basis of colony morphology and microscopic features. Tissue culture was negative for fungi. Computed tomography of the head was normal. The patient was started on liposomal amphotericin B (300 mg every 24 h, 5 mg/kg/day) intravenously, additionally to switch of antibiotics to ceftazidime (2 g twice daily) and amikacin (7.5 mg/kg daily) adjusted for renal function during 10 days. Given the unfavorable clinical symptoms, inflammatory parameters and radiographic findings (**Figure 2(b)**), it was added posaconazole (400 mg twice daily) intravenously and the dose of L-AmB was increased to 10 mg/kg/day. Having completed 14 days of treatment, partial radiographic improvement was evident and proven by control CT of the chest. The patient underwent new FB that revealed sharp decrease in the diameter of the left lung bronchus to 3 cm from the carina by prolapse of the outer wall with hyperemic and edematous mucosa and bronchus upper lobe occluded by partially macerated tissue. Additionally, the BAL isolated a *Methicillin-resistant staphylococcus aureus* sensitive to vancomycin and *Pseudomonas aeruginosa* sensitive to amikacin and meropenem. TBB revealed multiple broad non-septated, ribbon-like, right angle-hyphae consistent with Mucormycosis (Grocott technique and hematoxylin-eosin). It was carried out switch of antibiotics to meropenem (1 g twice daily) and linezolid (600 mg twice daily) adjusted to kidney function for 14 days while maintaining double antifungal therapy. With treatment optimization, partial clinical and imaging improvement was evident, and the patient underwent left pulmonary pneumectomy. It was identified a mass in the left upper lobe with substantial inflammatory changes of the pulmonary hilum and necrotic material that did not allowed dissection. Bacteriological and mycological examination of pleural fluid was negative. In the postoperative period, the patient was transferred to an Intensive Care Unit in acute renal failure,

severe hypoglycaemia and severe metabolic academia requiring continuous veno-venous hemofiltration, venous catheterization for hemodialysis and artery catheterization. The patient completed 4 weeks of liposomal amphotericin B (L-AmB) and posaconazole. After clinical stabilization, the patient experienced favorable evolution and was discharged. Admitted invasive pulmonary mucormycosis with partial response to double antifungal therapy with a significant component of repeated bacterial superinfection in a patient undergoing multiple rounds of antibiotics and then left pneumonectomy with favorable outcome. When last evaluated, 12 months following the initial presentation, the patient was asymptomatic, with a stable chest radiography (**Figure 1(c)**) and no evidence of relapse on CT of the chest.

3. Discussion

Pulmonary mucormycosis is a promptly progressive disease with high mortality and morbidity. Diabetes is the most common underlying condition in some case series, as described in our patient. Particularly, uncontrolled hyperglycemia and ketoacidosis are probably associated with development of mucormycosis in diabetic patients [7]. Our patient had the mentioned key predisposing factors concerning diabetes, and exposure by inhaling aerosolized mucor spores of an opportunistic microorganism from the environment, in a susceptible patient, may have been the infection pathway. No clinical history or chest imaging is specific for the diagnosis of pulmonary mucormycosis. This entity may present with several imaging findings, such as masses with a halo sign or a reversed halo-sign, consolidation with or without a cavitary or necrotic consolidation with an air-crescent sign, or solitary or multiples nodules and masses [8]. It has been reported sequential morphological changes in follow-up of pulmonary mucormycosis after anti-fungal treatment, namely mass or masses with a halo or reversed-halo sign on the initial CT scan followed by a decreased extent of surrounding ground-glass opacities with the development of internal necrosis [9]. In our case, a small opacity in the left upper lobe rapidly progressed to a large necrotic lesion, involving adjacent structures and surrounded by ground glass densification and interlobular septal thickening. Direct examination of sputum or BAL fluid is regularly nondiagnostic, but isolation of *Mucorales* organisms from such samples in a susceptible patient should be measured as a convincing evidence of infection additionally to clinical manifestations, as we promptly considered once the provisionally identification of *Mucor* was established. Concomitant fungal infections may also be identified.

Although the acknowledgment of risk factors, clinical and radiological findings may increase the possibility of an early recognition, the definite diagnosis is challenging to establish and frequently involves invasive techniques considered “gold standard” such as tissue biopsy, histological examination or *in vitro* culture [10] [11]. The histopathological identification of an organism may be the only evidence of infection, as it is known that culture may have no growth [12]. Identification of *Mucorales* species based only on morphological features is time-consuming, challenging, and involves knowledge. *Mucorales* organisms are often morphologically distinct from other filamentous fungi. Molecular identification has been applied to overcome the previously limitations. Rapid diagnosis is central for optimal therapeutic management, being delay an important cause of poor outcome. Subsequently, the diagnosis if frequently made postmortem. Distinction by direct examination may let treatment to be initiated. Occasionally, morphological features of *Mucorales* organisms may be atypical, mostly when therapeutic is initiated previously to tissue biopsy, reducing the dissimilarity from other filamentous fungi.

Mucormycosis management includes association between antifungal agents and surgery. Additionally, correction of the underlying condition predisposing the patient to the disease is also critical [13]. Concerning uncontrolled diabetes, metabolic abnormalities should be appropriately improved.

L-AmB is the first choice antifungal in a dose of 5 mg/kg/day, up to a maximum of 10 mg/kg/day usually for central nervous system infections. Additional pharmacological treatments include triazole posaconazole as promising salvage treatment. It has activity against *Mucorales* and can be used in combination with L-AmB, in patients intolerant to L-AmB, with refractory mucormycosis or as an oral stepdown strategy [5] [14]. Although there are concerns due to noteworthy necrosis of the affected tissue that borders the antifungals penetration and activity. Early surgical intervention is strongly advised.

Other treatments include iron chelators such as deferiprone and deferasirox; echinocandins in association with L-AmB; and recombinant growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) particularly for neutropenic and transplanted patients. Hyperbaric oxygen may be used in diabetic patients with mucormycosis, but most of the evidence is from case reports/series, which limits solid conclusions about this promising treatment [15]. The best management of mu-

cormycosis, in particular pulmonary mucormycosis is not known, improved by the lack of evidence of randomized clinical trials, conducing to overtoxicity and undertreatment. In the present case of life-threatening and refractory pulmonary mucormycosis by *Mucor*, combination of metabolic abnormalities correction, bacterial superinfection treatment, L-AmBin a maximum dosage of 10 mg/kg/day associated to posaconazole as a salvage treatment and an early surgical intervention constituted a complex and the most adequate treatment. Predictors of mortality or clinical response are equally not defined, but may be related to poor host response, namely neutropenia, delays in the diagnosis and limited available therapy [16]. With our case, we emphasize the importance of underlying comorbidities control, since uncontrolled diabetes favors rapidly fatal infections and a brief English-literature review of the few cases published to date resulted in the death of most patients with pulmonary mucormycosis in this context. West rengthen the importance of rapid and accurate suspicion and identification of the pathogen, mainly in susceptible patients, and a promptly multimodal approach to achieve a favorable outcome.

4. Conclusion

In our patient, the dual anti-fungal treatment combined with left pulmonary pneumectomy led to recovery from invasive pulmonary mucormycosis. Also, we take into consideration the repetitive bacterial superinfection that contributed to delay the favorable clinical evolution. This case signs a positive clinical outcome in an uncontrolled diabetic, treated with a combination of two antifungal agents (L-AmB and posaconazole) and surgery. As a relatively rare disease, invasive pulmonary mucormycosis is not yet entirely understood by the medical community and consequently enhancement of education about diagnosis, treatment and prevention is essential. This case highlights the importance of clinicians' awareness to early diagnosis, as well as combined antifungal treatment and adjuvant surgery as the ideal method of therapy with the greatest chance of cure.

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