



## Case Report

## A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient

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## ABSTRACT

A patient with well-controlled type 2 diabetes mellitus developed a severe pulmonary infection secondary to *Rhizopus* spp. after receiving short courses of corticosteroids for a respiratory tract infection. He recovered after an aggressive surgical intervention and treatment with isavuconazole. Patients on chronic corticosteroid therapy have a higher risk for pulmonary mucormycosis, but there are much fewer reports of mucormycosis occurring in patients after only short courses of steroid therapy.

## 1. Introduction

Mucormycosis is an invasive and potentially life-threatening opportunistic fungal infection. The term “mucormycosis” describes infections caused by ubiquitous, saprophytic, and filamentous fungi in the subphylum Mucoromycotina. Species belonging to the *Rhizopus*, *Mucor*, and *Lichtheimia* (*Absidia*) genera are most commonly implicated. The primary mode of acquisition is through the inhalation of sporangiospores present in the environment. Traumatic inoculation and oral ingestion are other possible forms of transmission [1].

Incidence and prevalence estimates of mucormycosis are limited by factors inherent to a rare disease that is difficult to diagnose pre-mortem. Mucormycosis, as opposed to other filamentous opportunistic molds, is able to cause disease in a more heterogeneous patient population. The predisposing conditions vary geographically with diabetes mellitus being the most common risk factor in Asia and hematological malignancies with prolonged neutropenia and transplant recipients being the most important ones in the Western world. There is an association between the predisposing condition and the clinical presentation. For example, the rhino-orbito-cerebral form is most commonly seen in the setting of poorly-controlled diabetes. Pulmonary mucormycosis typically affects hematopoietic stem cell transplant recipients or those with prolonged neutropenia and is usually associated with concomitant involvement of the sinuses and a high case fatality

rate [2].

Isolated pulmonary mucormycosis is a very rare entity. Since the first report of this disease in 1876, there has been a handful of reviews describing the clinical presentations and risk factors associated with pulmonary mucormycosis. One of the first reviews consisted of 87 cases reported between 1977 and 1999 followed by a more recent review consisting of 92 cases reported between 2006 and 2016. While diabetes and hematological malignancies were the most common risk factors noted in both reviews, there was also a significant portion (12–13%) of patients who had no apparent underlying comorbidities [3,4]. In the largest comprehensive review of the literature of 929 cases, pulmonary involvement constituted more than one-half of all sites of infection in patients with malignancy and recipients of bone marrow transplants. The overall mortality of pulmonary mucormycosis was 76% and 95% when the diseases was disseminated [5]. We describe a patient with well-controlled diabetes that developed a severe pulmonary infection due to *Rhizopus* spp. after a relatively short course of high doses of steroids. This case highlights the importance of restricting steroids to well-established indications and to closely monitor for development of complications related to their use.

## 2. Case

A 66-year-old man with well-controlled type 2 diabetes mellitus

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(hemoglobin A1c of 6.4) was initially seen by a physician in mid-January at a local urgent care clinic for evaluation of a two-week history of a productive cough, fever, and malaise. The day he first presented to the clinic with these symptoms will be defined as “day 0” in this report. He was diagnosed with bronchitis and given a course of 60 mg of prednisone daily for five days in addition to a three-day course of azithromycin. The patient took the medications as prescribed but due to lack of improvement he returned to the clinic on day 3 with worsening cough. At that time, he was diagnosed with influenza A via molecular testing of a nasopharyngeal swab. A chest X-ray showed no abnormalities. Oseltamivir was also prescribed and two different formulations of steroids were administered - 80mg of methylprednisolone intravenously and an intramuscular injection of 8mg of dexamethasone.

He returned to the clinic on day 9 due to worsening cough and fever. He was given another course of daily prednisone at a dose of 40 mg for 5 days. The patient and wife reported that steroids had caused persistent elevation of the blood glucose level in the 200–300 mg/dl range. The patient presented to the emergency department of a local hospital on day 12 due to continued cough, fever and now with 4.5kg weight loss. He was found to have severe hyperglycemia without diabetic ketoacidosis (glucose > 500 mg/dl). He was hospitalized and imaging of the chest obtained on day 13 showed a cavitory lesion measuring 4.7 cm × 3.6 cm within the superior segment of the left lower pulmonary lobe (Fig. 1A and B).

He was treated with broad-spectrum antibiotics and discharged home 5 days after admission. Results of a sputum culture showing *Rhizopus* spp. became available on day 22. He was started on voriconazole on day 24 by his primary care physician, likely without the realization that this would provide inadequate coverage for *Rhizopus* spp. A repeat chest X-ray obtained at a post-hospitalization follow-up visit in his primary care physician's clinic on day 38 showed enlargement of the cavitory pulmonary lesion in the superior segment of the left lower lobe. The patient was then referred to Pulmonology. Hospital admission to evaluate for surgical intervention and intravenous antifungal therapy was offered, but given his minimal symptoms, he opted for outpatient antifungal therapy. He was switched to isavuconazole, and a follow-up computed tomography (CT) of the chest was arranged. CT of the chest was done on day 58 and showed significant progression of the cavitation with air-fluid levels and a new pleural effusion (Fig. 1C) prompting another hospital admission on day 59.

On this second hospital admission, his vital signs were within normal range with the exception of hypoxemia that was corrected with 3 L of O<sub>2</sub> through nasal cannula. His physical exam was remarkable for decreased breath sounds over the left lower base, rales on both bases, and egophony noted on the left upper and mid lobes. Bloodwork revealed glucose levels in the 140–160 mg/dL range and a creatinine at his baseline (1.48 mg/dL). The hemoglobin A1c measured was 7.3.

A magnetic resonance imaging (MRI) of the head and sinuses showed no evidence of cerebral or sinus infection. The patient was initially treated with liposomal amphotericin B at a dose of 5mg/kg daily on day 60. The patient underwent a left thoracotomy, left lower

lobectomy, with *en bloc* wedge of left upper lobe, and latissimus muscle flap coverage of the bronchial stump on the 5th day of hospitalization (day 64) without complications. A sputum culture obtained at admission showed *Rhizopus* spp. and the resected lung specimen showed hyphae that were morphologically consistent with mucormycosis (Fig. 2A–D). The intra-operative fungal culture failed to grow the mold. The post-operative course was complicated by a rapidly rising creatinine prompting discontinuation of the polyene after six doses – discontinued one day after surgery. He then received loading doses of isavuconazole and continued on 200 mg PO daily afterwards.

The patient was discharged on isavuconazole and off oxygen on day 73. He had a follow up CT of the chest on day 184 that showed no abnormalities other than expected postoperative findings. The isavuconazole was discontinued at that time and the patient continued to do well at follow-up 9 months after stopping the azole (day 454).

### 3. Discussion

Mucormycosis is an opportunistic fungal infection characterized by its angioinvasive property often resulting in tissue necrosis and thrombosis. In immunocompromised hosts, the course is usually rapid and devastating. In patients with diabetes mellitus the course can be more subacute as exemplified in this case.

Poorly controlled diabetes has an established and strong correlation with invasive mucormycosis. Diabetes mellitus was identified in 36% of patients and was the most common predisposing condition in one of the largest epidemiological studies conducted thus far [5]. Hyperglycemia impairs chemotaxis and the oxidative and non-oxidative fungicidal mechanisms used by phagocytic cells - the main defensive mechanism against mucormycosis. Hyperglycemia also increases the expression of GRP78 (a 78 kDa glucose-regulated protein) which acts as the endothelial receptor for the ligand (spore-coating protein homolog) used by the agents that cause mucormycosis [6–8]. In states of acidosis related to hyperglycemia, free iron becomes readily available in the serum. Mucorales can acquire this excess endogenous iron through siderophores (low-molecular-weight chelators) or iron permeases enhancing their virulence [9].

Corticosteroids, on the other hand, cause impairment in the migration, ingestion, and phagolysosome fusion of bronchoalveolar macrophages. Coupled with the potential adverse effect of steroid-induced hyperglycemia, a diabetic patient receiving corticosteroids is exceptionally vulnerable to the development of mucormycosis. There are few case reports of pulmonary mucormycosis resulting from short courses (5–14 days) of steroids for exacerbations of chronic obstructive disease in the setting of well-controlled diabetes mellitus [10–13]. Our case specifically exemplifies that profound and sustained immunosuppression is not necessarily a requirement for mucormycosis to develop. The patient's diabetes was well-controlled (with documented hemoglobin A1c < 7.0), but several short courses of high-dose steroids precipitated a potentially life-threatening pulmonary invasive fungal infection requiring an aggressive surgical procedure. Additionally, our

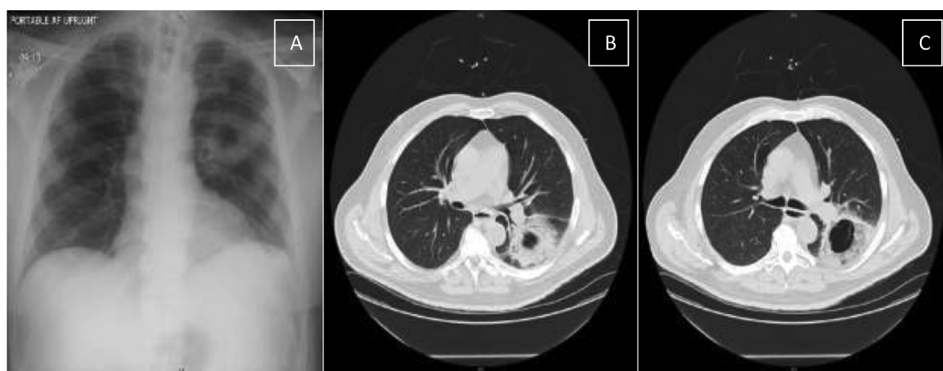
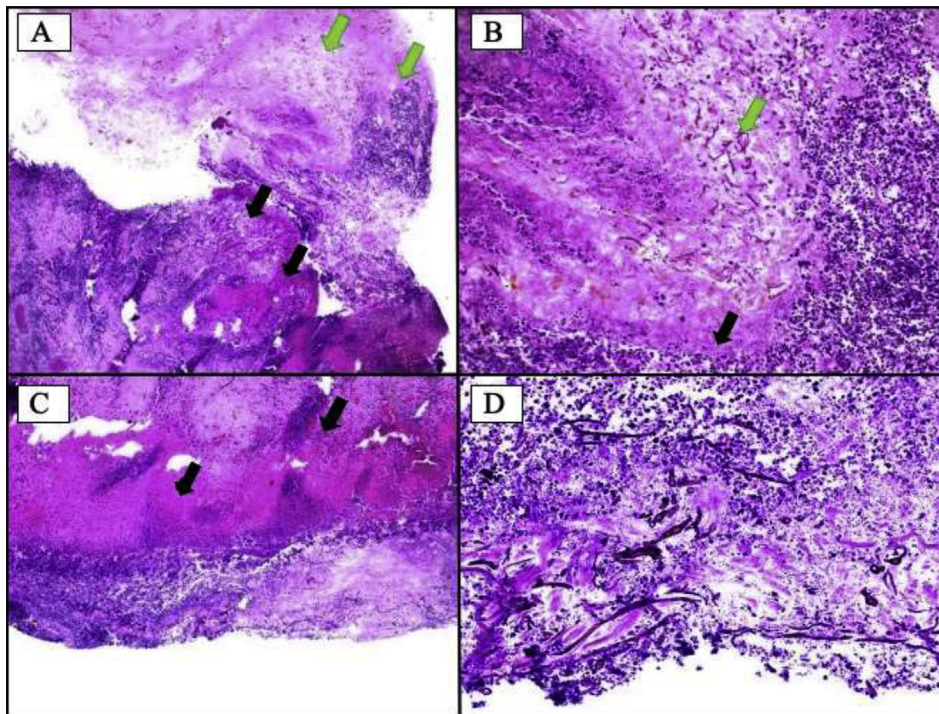


Fig. 1. A. Chest x-ray of thick-walled cavitory lesion noted in superior segment of left lower lobe.

B. CT chest without contrast showing consolidation in the superior segment of the left lower lobe with thick walled central cavitation. C. CT chest without contrast showing significant progression of consolidation in the superior segment of the left lower lobe with thick walled central cavitation.



**Fig. 2.** A. Wedge resection of cavitary lung mass: H&E section shows a well circumscribed granuloma with central necrosis (green arrow). The granulomatous wall is infiltrated by both acute and chronic inflammatory cells (black arrows). B. Wedge resection of cavitary lung mass: H&E section of the central necrotic area contains abundant ribbon-like aseptated fungal elements with occasional branching (green red arrows) admixed with necrotic debris and chronic inflammatory cell infiltrates (black arrows). C. Wedge resection of cavitary lung mass: H&E section shows a well-circumscribed granuloma with central necrosis (white arrows). The granulomatous wall is infiltrated by both acute and chronic inflammatory cells (black arrows). D. Wedge resection of cavitary lung mass: H&E section at higher magnification shows abundant aseptated ribbon-like fungal elements. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

patient's development of pulmonary mucormycosis seemed to have transpired within a time-frame of roughly only two to three weeks. The indication for steroid use is unclear to us and no information regarding their use in this particular case could be obtained. Given the ubiquitous use of glucocorticoids for a variety of ailments in the primary care setting, this is likely not a unique occurrence. There are several reports that suggests that influenzae infection may be an independent risk factor for fungal pneumonia, specifically invasive pulmonary aspergillosis [14,15]. There is also evidence that corticosteroid therapy in patients with influenzae have been linked with invasive fungal infection. While there have been a few reports of post-influenzae infection with pulmonary mucormycosis - unlike pulmonary aspergillosis, there seems to be a less established correlation reported in the literature [15–17].

The choice of voriconazole when the initial sputum culture result became available is not supported by the available literature and the reason for its use is unclear [18]. Our case, along with the several recently recorded in the literature, emphasize the need for physicians to be more judicious in the use of corticosteroids in the outpatient and inpatient setting, especially in the diabetic population or those with other immunosuppressive comorbidities. Even short-duration, high-dose regimens that in the past have been considered fairly harmless and low-risk for opportunistic infections can lead to life-threatening infectious complications [19,20].

#### Declaration of competing interest

There are none.

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There are none.

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