Pulmonary mucormycosis in a patient with Crohn disease on immunosuppressive medications including infliximab

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CASE PRESENTATION

A 68-year-old man presented to hospital with a two-day history of increasing shortness of breath, left-sided pleuritic chest pain and chills. His medical history was significant for longstanding Crohn disease (>55 years) requiring multiple bowel resections in the 1970s in addition to high-dose corticosteroid therapy. For the past five years, he had been maintained on infliximab with only low-dose steroids for iatrogenic adrenal insufficiency. Additional medical problems included short gut syndrome, hypothyroidism and bronchiectasis; there was no history of diabetes. He experienced two hospital admissions in the preceding six months for pneumonia, one of which was due to *Pneumocystis jirovecii* confirmed by open lung biopsy. His medications on this admission included budesonide 6 mg orally three times daily, azathioprine 100 mg orally twice daily, infliximab 600 mg intravenously every four weeks, levothyroxine 25 µg orally daily, atovaquone 1500 mg orally daily, and salbutamol and ipratropium inhalers as needed. His most recent dose of infliximab was one month before admission.

A physical examination revealed signs of consolidation in the left lung. His complete blood count included a white blood cell count of 15.2×10^9 cells/L, predominantly composed of neutrophils (14.3×10^9 cells/L). Electrolytes were remarkable for a blood sugar level of 32.5 mmol/L, with a negative screen for ketones. Arterial blood gas tests revealed a pH of 7.46 with a CO₂ level of 26 mmol/L. His albumin level was 18 g/L (normal three months previously). A chest radiograph was suspicious for a cavity in the left upper lobe; a subsequent computed tomography scan of the chest confirmed a cavitary lesion measuring 10 cm in maximum diameter extending to the pleural surface, as well as extensive left upper and lower lobe consolidation (Figure 1A). He was diagnosed with recurrent pneumonia complicated

by lung abscess formation and was started on piperacillin-tazobactam, azithromycin and stress-dose corticosteroids.

Sputum cultures on admission grew *Klebsiella pneumoniae*, while blood cultures were positive for *Burkholderia cepacia*. The patient was assessed by the infectious disease service, who recommended a change in the antibiotic regimen to meropenem as well as consideration of percutaneous drainage of the lung abscess. A serum hemoglobin A_{1c} level drawn three days after admission was 9.3% and the endocrinology service was consulted for management of new-onset diabetes mellitus.

Despite treatment, the patient continued to experience fluctuating shortness of breath and pleuritic chest pain. His peripheral white blood cell count remained elevated, and chest imaging showed no resolution of the lung abscess. A bronchoscopy was performed.

DIAGNOSIS

Bronchoscopy ruled out an endobronchial obstruction. Washings from the lingula were culture negative; however, cytology revealed the presence of fungal elements suspicious for *Mucor/Rhizopus* or *Aspergillus* species. Subsequent percutaneous drainage of the lung abscess was nondiagnostic. He underwent a left upper lobectomy that confirmed a lung abscess due to *Mucor/Rhizopus* species with pathological evidence of tissue invasion involving the chest wall and mediastinum (Figure 1B). Fungal cultures were ultimately negative.

Despite reduction in the patient's immunosuppression to maintenance corticosteroids and combination therapy with intravenous amphotericin and micafungin, the patient's condition deteriorated progressively and he died three months after the initial diagnosis of mucormycosis. Retrospectively, there was no exposure history, including exposure to hospital construction, which could account for his

Figure 1) Left panel Computed tomography image of the chest (lung window) showing extensive consolidation of the left lung with cavitation extending to the pleural surface. Right panel Photomicrograph of one region of the cavity showing the surrounding rim of necrotic lung tissue. A prominent pulmonary artery (A) is partially necrotic and infiltrated by fungal hyphae (asterisk: cavity lumen; B: bronchiole). Inset: High-power photomicrograph of the hyphae of the *Mucor/Rhizopus* species. The hyphae are pauciseptate, of variable thickness and demonstrate a 'folded tissue' or 'ribbon-like' appearance. Some of the branches can be seen originating at right angles from the parent structure

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infection. Although his ferritin level was 2238 pmol/L in the month before hospital admission, there was no evidence of iron overload, with a serum iron level of 12 µmol/L and iron saturation of 25%.

DISCUSSION

Mucormycosis refers to a number of deep-seated invasive infections caused by fungi in the order *Mucorales*. These pauciseptate fungi are found ubiquitously throughout the environment but evoke a strong immune response in the normal healthy host, protecting the majority of exposed individuals from developing disease (1). It is only after the immune system has become compromised that invasion and disease can occur. Patients at highest risk are individuals with uncontrolled diabetes mellitus or prolonged neutropenia; those taking high-dose corticosteroid therapy; or those who are hemodialysis dependent and require iron chelation therapy with deferoxamine (2). In our patient, his newly detected diabetes would have contributed to his infection risk because phagocytes in a hyperglycemic environment are known to exhibit impaired chemotaxis and killing responses to *Mucorales* spores and hyphae (1).

Previously a rare condition, increases in the incidence of mucormycosis have been documented in both developed and developing countries (2). This change has been postulated to be due to a growing population of immunosuppressed patients, changes in medical treatment or prophylaxis for those at the highest risk for opportunistic infection, or improvement in diagnostic techniques for organisms that are traditionally difficult to culture (2). *Mucorales* are fragile and fragmentation of their large branching hyphae can render specimens nonviable. As a result, specimens that are not processed via grinding but instead either treated with a process known as 'stomaching' to homogenize the tissues or sliced yield better recovery (3).

The antitumor necrosis factor (TNF) agents, including infliximab, are potent immunosuppressive medications that are licensed for the treatment of a variety of autoimmune diseases including Crohn disease (4). Postmarketing surveillance has detected that patients treated with these drugs are at risk of a number of opportunistic infections. Reactivation tuberculosis was initially the primary opportunistic infection of concern because TNF is important in the formation and maintenance of granulomas (5,6). However, TNF has other roles in the host defence system – including inducing phagosome activation and recruiting neutrophils and macrophages to the site of infection – and, over time, there has been an expansion in the 'black box warning' for patients taking anti-TNF agents to include other opportunistic pathogens such as *Listeria monocytogenes* (6,7). Although the increased risk is predominantly for well-known intracellular pathogens, it is not currently clear whether other pathogens, such as *Mucorales*, also pose a specific risk.

Even with the advent of newer treatment regimens for fungi in general, mucormycosis still portends a dismal prognosis (8). Effective therapy relies on a combination approach with reduction in immunosuppression and aggressive debridement at the site of infection paramount to cure. Medical treatment is more limited because *Mucorales* are intrinsically resistant to most of the available antifungals.

Amphotericin is considered to be the first-line agent for treatment, with multiple uncontrolled studies suggesting that liposomal preparations are superior to conventional deoxycholate (2). This may be because patients often require higher doses (ie, 5 mg/kg/day to 10 mg/kg/day) than needed for fungi such as *Aspergillus* species, and liposomal amphotericin is better tolerated. Posaconazole – the only triazole with activity against *Mucorales* – can be used as salvage therapy and has demonstrated benefit in small series (2). Because it is only available as an oral suspension, absorption can be highly variable among patients but improves with concomitant food intake (9). There is a theoretical risk of antagonism if these two agents are combined; however, combination therapy is sometimes used for exceedingly ill patients.

Echinocandins are not active against *Mucorales*. However, *Rhizopus oryzae* does possess the target enzyme for echinocandins and has been tried as a therapy in combination with amphotericin. A single retrospective study involving 41 patients with disseminated disease (10) suggested a survival benefit, although additional data are necessary to confirm these findings. In our patient, combination therapy with an echinocandin was chosen because the patient was already known to have a short gastrointestinal tract with potential absorption issues and, furthermore, was experiencing ongoing issues with gastrointestinal bleeding and diarrhea throughout his hospital stay.

We acknowledge that our patient had multiple risk factors that contributed to an overall high net state of immunosuppression. He was on high-dose azathioprine, had newly diagnosed diabetes mellitus and had been pulsed with steroids during his admission. However, we believe this case adds to the literature demonstrating the risk of opportunistic infections other than tuberculosis in patients undergoing anti-TNF therapy. These infections can be remote from the site of the underlying disease process that necessitated anti-TNF therapy and can be exceedingly difficult to diagnose. In a patient receiving an anti-TNF agent, such as infliximab or multiple immunosuppressants, failure to respond to conventional management for pneumonia or lung abscess should prompt careful reconsideration of all potential pathogens including angioinvasive fungi such as *Aspergillus* and the *Mucorales*. Recognizing the difficulty of culturing these organisms from conventional microbiological specimens, early consideration of invasive diagnostic procedures, such as percutaneous or open biopsy, is warranted.

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