Case Report

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TANAFFOS

Fatal COVID-19-Associated Pulmonary Aspergillosis Due to *Aspergillus niger* Complicated By Pneumothorax: A Case Report

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COVID-19-associated pulmonary aspergillosis (CAPA) carries high mortality. *Aspergillus niger* is not commonly associated with CAPA. A middle-aged woman presented with cough, fever, and dyspnea for ten days and was subsequently diagnosed with COVID-19. She was mechanically ventilated and given methylprednisolone and broad-spectrum antibiotics. The initial computed tomography pulmonary angiogram (CTPA) was negative for pulmonary embolism, yet the patient's condition continued to worsen. A repeat CT scan of the thorax on day 17 revealed two new cavities. Ensuing tracheal culture was positive for *Aspergillus niger*, and later complicated with pneumothorax. She was treated with amphotericin B, but her clinical course was complicated by a pneumothorax, for which a chest tube was inserted. Despite all efforts, the patient eventually succumbed. *Aspergillus niger* infection can have devastating consequences in the setting of severe COVID-19 infection. It raises urgent questions about the need for antifungal prophylaxis. Pneumothorax is a potential complication of CAPA, especially when the cavities are very peripheral.

Keywords: COVID-19-Associated Pulmonary Aspergillosis; Pneumothorax; *Aspergillus niger*; Case Report

INTRODUCTION

COVID-19-associated pulmonary aspergillosis (CAPA) is a well-described entity with a high mortality rate of nearly 60% (1). In Malaysia, there is only one case series of CAPA available (2), while globally, cases of CAPA complicated by pneumothorax have been reported sporadically (3, 4). In this study, we report a 61-year-old woman who developed fatal CAPA due to *Aspergillus niger*, complicated with pneumothorax.

CASE SUMMARIES

A woman in her early 60s with underlying ischemic heart disease presented with cough, fever, and dyspnea for ten days. On examination, she had a blood pressure of 117/59 mmHg, pulse rate of 75 b/m, oxygen saturation of 86% on bilevel positive airway pressure, and was tachypneic with a respiratory rate of 26 breaths per minute. Laboratory results were significant for leukopenia (2.97 x 10^9/L), elevated C-reactive protein (44.5 mg/L), and positive real-time reverse transcriptase-polymerase chain reaction for SARS-COV-2. The baseline chest radiograph showed mild, right-sided peripheral ground-glass opacities (Figure 1A). She was admitted to the intensive care unit and received methylprednisolone for five days. However, her condition worsened, and she was intubated on day 10, with antibiotic escalation to meropenem. She was not prescribed any anti-viral medication because of transaminitis. Computed tomography pulmonary angiography (CTPA) performed on day 11 revealed bilateral ground-glass and consolidative changes with no

evidence of pulmonary embolism. Given worsening leukocytosis, increasing inflammatory markers, and new cavitations seen in a repeat chest radiograph on day 16 (Figure 1B), a repeat HRCT was done. It showed organizing pneumonia changes, and new thick-walled cavities at the medial segment of the right middle lobe with a rounded mass within this cavity measuring 1.6 x 1.7 x 1.5cm; another similar cavity with a rounded mass within was found at the anterior segment of left upper lobe measuring 2.2 x 3.1 x 2.6cm (Figure 2A and B). Tracheal aspirate fungal culture was positive for *Aspergillus niger*, albeit after three days of culture inoculation, the ensuing serum Aspergillus antigen was positive. Other tracheal aspirate cultures and blood cultures were negative. As Voriconazole was not available, Amphotericin B was administered. Unfortunately, the patient developed a right tension pneumothorax on day 22 of admission for which a chest drain was inserted (Figure 1C). No HRCT was repeated as the patient's condition became progressively unstable. The patient succumbed on Day 24 of admission.

Figure 1. Comparison of serial chest radiograph on admission (A), at day 16 (demonstrating new cavitary lesions) (B), and at day 22 (post-chest tube insertion) (C) of admission

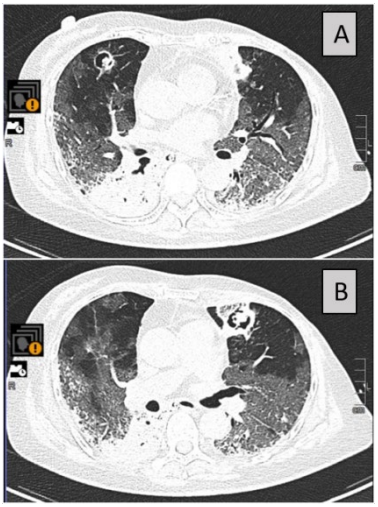

Figure 2. Computed tomography of the chest (axial view) demonstrates cavitation with a rounded mass within the right middle lobe (A) and left upper lobe (B)

DISCUSSION

Aspergillus niger is one of the rarer causes of CAPA consisting of 4% of all CAPA, according to meta-analysis data (1). Before the COVID-19 era, *Aspergillus niger* was a minority causative organism of invasive pulmonary aspergillosis (IPA) (5). CAPA adversely affects COVID-19 mortality rates (6). It is not uncommon for CAPA to occur in COVID-19 patients without significant risk factors (7). The administration of high-dose potent corticosteroids likely increased the risk of secondary infection in our patient. (6).

The median time to diagnosis of CAPA is eight days (1). In contrast, our patient was diagnosed with CAPA on day 17. Possible reasons for such a delay may include a robust immune system, given that our patient was neither previously immunocompromised nor had any comorbidities. Another reason is that *Aspergillus niger* is difficult to isolate in conventional culture medium (8).

There have been calls to initiate antifungal prophylaxis in COVID-19 patients, specifically inhaled amphotericin B, based on previous practices of using inhaled amphotericin B in lung transplant patients (9). Thus far, the role of antifungal prophylaxis is not established but is a plausible concept. Guidelines on IPA fall short of prophylaxis, instead recommending early initiation of antifungal therapy in patients with high clinical suspicion of IPA (10).

Voriconazole is the recommended first-line treatment for IPA (11), while isavuconazole and liposomal amphotericin B are the recommended alternatives (12). Liposomal amphotericin B is an effective alternative treatment option, but it carries the risk of renal insufficiency (12). This concern is particularly relevant for patients infected with SARS-CoV-2, which has shown renal tropism and has been described as a frequent cause of kidney injury (13).

Pneumothorax associated with CAPA has been reported (3,4). We postulate that our patient's pneumothorax was due to the peripheral nature of the cavity thus leading to a breach of the pleura. Another possible etiology of pneumothorax in our patient is barotrauma, given that the patient was mechanically ventilated; however, the ventilation settings were lung-protective at the time of pneumothorax occurrence (14).

Early diagnosis and treatment can reduce CAPA-related mortality, with some authors recommending prophylaxis or intensive screening protocols for at-risk patients (15). In one study from the United Kingdom, a proposed screening protocol with early antifungal treatment demonstrated a significant survival benefit (16).

CONCLUSION

The severe consequences of Aspergillus niger infection in the setting of severe COVID-19 infection raise urgent questions about the need for antifungal prophylaxis. Meanwhile, pneumothorax is a potential complication of CAPA, especially in those with peripheral cavities. Clinicians must have a high suspicion of CAPA in an intubated patient who does not improve clinically and biochemically.

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