

## Case Report

# Acute Pulmonary Aspergillosis as a Severe Complication of Influenza, Pneumococcal Pneumonia, and *Staphylococcus aureus* Bacteremia in ICU

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Received 31 August 2019; Revised 3 November 2019; Accepted 26 November 2019; Published 16 December 2019

Academic Editor: Gloria Taliani

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**Background.** Acute aspergillosis is a disease with dramatic progression and high mortality if not treated rapidly. However, diagnosing and treating is challenging, as the risk factors are not fully understood. **Case Presentation.** A fifty-three-year-old woman without any comorbidities was admitted to hospital due to high fever. Infections with influenza and pneumonia and *Staphylococcus aureus* bacteremia were diagnosed. The patient improved at first due to antimicrobial therapy; nine days after admission, her clinical condition deteriorated again, and she was transferred to ICU due to septic shock accompanied by respiratory failure, necessitating mechanical ventilation and high-dose catecholamine support. A CT scan showed a resolving inflammatory infiltrate bilateral caverns with markedly thickened walls. A culture from a bronchoalveolar lavage grew *Aspergillus fumigatus*. Galactomannan testing was positive in a bronchoalveolar lavage sample, and beta-D-glucan was positive in serum. Antifungal therapy with voriconazole and intermittent isavuconazole due to renal failure was performed, followed by a surgical resection of the caverns. Patient's recovery was complicated by several severe bleeding episodes in the lungs. However, the patient showed full recovery and was discharged after 109 days in hospital. **Conclusions.** This case report highlights multiple complications of influenza and the difficulties of diagnosing and treating acute pulmonary aspergillosis. Furthermore, it stresses the importance for further studies to deepen the understanding about the association between influenza and aspergillosis and to shed further light on adequate therapy.

## 1. Introduction

Acute aspergillosis is a disease with dramatic progression and high mortality if not treated rapidly [1, 2]. The fungal spores of aspergillus are ubiquitous, and most people breathe in fungal spores every day. In people with impaired innate immune system, the fungal spores can overcome the barrier of the respiratory tract and cause a pulmonary infection, known as acute pulmonary aspergillosis (APA). Known risk factors for development of APA are systemic therapy with glucocorticoids or other immunosuppressive drugs, haematological diseases, stem cell transplants, HIV, liver cirrhosis, and sepsis which lead to an impaired cell-mediated immune system [1, 3].

In 2018, Schauwvlieghe et al. [4] published a study discussing infection with influenza as a risk factor of APA.

They evaluated 432 patients admitted to seven ICU wards with respiratory failure and confirmed influenza infection and pulmonary infiltrates on imaging. The overall incidence of APA was 19%, and for immunocompromised patients, it was as high as 32%. The overall mortality of patients with APA was significantly higher (51%) than that of patients without APA (28%).

We report the case of a patient with a severe course of influenza complicated by acute pulmonary aspergillosis.

## 2. Case Presentation

A fifty-three-year-old woman without any comorbidities working as a cleaner came to the outgoing clinic with fever and malaise. Influenza A was diagnosed (positive PCR from nasopharyngeal), and therapy with oral oseltamivir was

prescribed which led to a rapid drop of fever and improvement of patient's well-being. However, four days later, the patient suffered from progressive dyspnoea and rising temperature and was admitted to the department of infectious diseases. Diagnosis of pneumococcal pneumonia was made (positive urinary antigen test and pulmonary infiltrates in the right lung on the chest X-ray). Therapy with intravenous penicillin G and azithromycin was instituted and led to improvement of her symptoms and inflammation parameters over the first 3 days.

Four days after admission, she had a new onset of fever (39.5°C), C-reactive protein increased to 297 mg/L, and leucocyte value increased to 14.3 G/L therapy was switched to piperacillin/tazobactam. Since *Staphylococcus aureus* was detected in blood culture and tracheal secretion; one day later, cefazoline was added to therapy. Three days thereafter, blood cultures were sterile. However, nine days after admission, her clinical condition deteriorated again, and she was transferred to the intensive care unit with septic shock and respiratory failure, necessitating mechanical ventilation and high-dose catecholamine support. A CT scan showed bilateral caverns (diameter up to 5 cm) with markedly thickened walls (see Figure 1). The differential diagnoses included tuberculosis and septic emboli due to *Staphylococcus aureus* bacteremia and invasive aspergillosis. Three consecutive negative PCRs and cultures ruled out tuberculosis. Blood cultures remained sterile, and on transoesophageal echocardiography, there was no sign of endocarditis. A culture from a bronchoalveolar lavage (BAL) grew *Aspergillus fumigatus*. Galactomannan (GM) testing was negative in serum, but positive in a BAL sample ((optical density (ODI) of 5.5)), and beta-D-glucan (BDG) was positive in serum (250 pg/ml).

Therapy with voriconazole IV was started (loading dose 400 mg twice daily for one day and then 250 mg every 12 hours). Serum levels of voriconazole were checked (via high-performance liquid chromatography) every third to fourth day and maintained with large fluctuations within 2–6 mg/L. After day 3 of therapy, the dose of voriconazole was increased to 300 mg every 12 hours due to borderline low serum level (2.1 mg/L).

Tracheostomy was performed for weaning.

The patient's state improved slowly: the fever ceased on day 16, support with catecholamines was stopped on day 19, and weaning was successful on day 62 of therapy. To control therapy success, CT and GM testing were performed. A CT scan performed two weeks after the initiation of antifungal therapy showed decreasing diameters of the caverns (maximum 4.3 cm). GM testing of BAL also showed a decrease (ODI 4.1). Weaning was complicated by a severe delirium, probably caused on the one hand by the sepsis and ICU stay and the high doses of sedatives and on the other hand, the high doses of voriconazole. The voriconazole serum level was 5.4 mg/L at time of development of delirium. On day 18 of therapy, the patient also developed acute kidney failure resulting in the need for continuous renal replacement therapy (CRRT). Due to acute kidney failure and delirium, antifungal therapy was switched to isavuconazole IV 372 mg once daily.

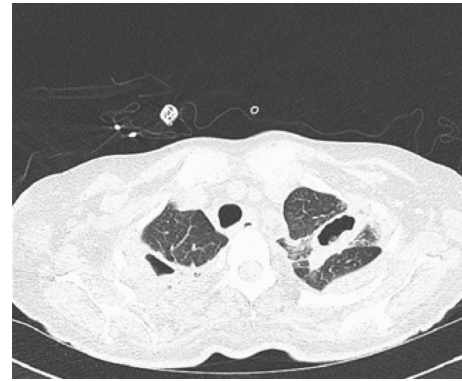


FIGURE 1: CT scan showing bilateral caverns.

After this, a rapid beneficial clinical response was seen. The delirium subsided, and physiotherapy was started. Nine weeks after admission, the patient was stable without mechanical ventilation. The renal function slowly recovered, CRRT was stopped (day 45), and as soon as the estimated creatinine clearance was >50 ml/min, antifungal therapy was switched back to voriconazole. The start doses of voriconazole were 300 mg twice daily. Serum levels were in the targeted range (2.8–3.9 mg/L). GM levels in BAL decrease further (ODI 1.7), and CT scan showed decreasing size of caverns.

The patient's recovery was complicated by several bleeding episodes in the lungs, which could be managed with tranexamic acid and supportive measures. Acute surgical intervention was not necessary. The patient was discharged from our ICU after a stay of 109 days and continued taking voriconazole 200 mg twice daily orally. After a 4-week rehabilitation, a control CT scan was performed. Serum levels of voriconazole were checked once a week and were always in the recommended range. Due to persistence in size of caverns despite antifungal therapy, surgical resection of the cavern in the right pulmonary lobe was performed, followed by elimination of the cavern in the left lung three weeks later. Therapy with voriconazole was suspended two months after surgery. The patient made a full recovery after a total of 167 hospital and rehabilitation days and returned to work over 1 year (397 days) after the onset of influenza.

### 3. Discussion

This case report highlights multiple complications of influenza with a dramatic clinical course. A summary of patient's history is shown in Figure 2. After a rather mild course of influenza, the patient developed pneumococcal pneumonia requiring hospital admission and later *Staphylococcus aureus* bacteremia. Literature described bacterial coinfection as complications of an infection with influenza with a prevalence of 11–33% [5]. The most frequently detected bacteria were found to be *Streptococcus pneumoniae* and *Staphylococcus aureus* [5].

Later, the patient suffered from acute invasive aspergillosis. Influenza and pneumonia were identified as key factors in the development and progression of this complication.

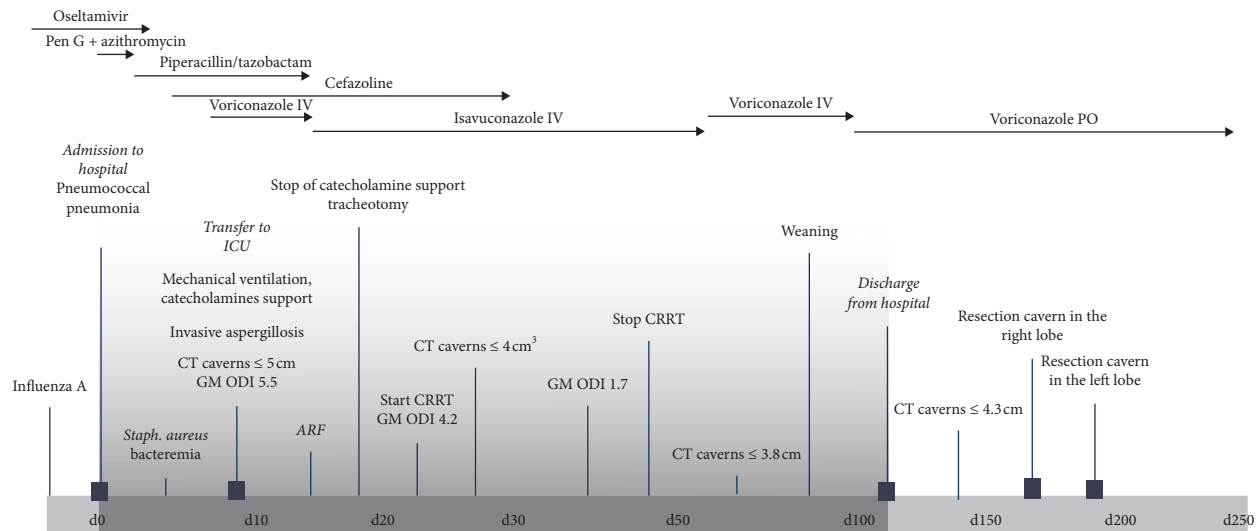


FIGURE 2: Summary of patient's history with given antimicrobial therapy. ICU: intensive care unit; GM: galactomannan; ARF: acute renal failure; CRRT: continuous renal replacement therapy.

The pathophysiology of how a preceding infection with influenza facilitates APA is not yet fully understood. Suppression of macrophage and T-cell activity by the influenza virus itself or a strong immune response triggered by a severe influenza infection leading to high production of cytokines suppressing the innate immune response have been proposed as possible mechanisms [2]. In addition, some single nucleotide polymorphism codings for Pentraxin 3 (PTX3) have been shown to be associated with the development of APA [2]. The influenza virus induces PTX3, which is an important component of the innate immune response against aspergillus.

The diagnosis of APA can be challenging and must be multimodal. It includes thoracic imaging [1, 3, 6]. In our case, the CT scan showed a typical manifestation; however, APA can present in several ways, e.g., as caverns, macronodules, pleural effusion, or tracheal or bronchial wall thickening [6]. Biopsy of the fungal lesion is the diagnostic measure with the best sensitivity for detection of aspergillus [3], but was not performed in this patient due to her hemodynamic and respiratory instability. BDG in serum was highly positive suggesting a fungal infection; however, the specificity for aspergillus is low [7, 8]. Not surprisingly, GM in serum was negative, given that the positive predictive value, especially in nonneutropenic patients, is low [9]. Therefore, we performed bronchoscopy, which yielded a positive GM result. GM has a much higher sensitivity and specificity in BAL than in serum [3].

We established the recommended 1<sup>st</sup> line anti-infective therapy with voriconazole. Later, we switched to isavuconazole, due to following considerations:

First, isavuconazole has been shown to be noninferior to voriconazole [10].

Secondly, isavuconazole causes fewer adverse effects, including neurological side-effects such as hallucinations [9]. Voriconazole might have contributed to the delirium that our patient was suffering from. The voriconazole serum levels varied widely. In the first week, low

borderline serum levels were measured up to 2.1 mg/L, and after increase of doses, the patient developed delirium. The serum level was up to 5.4 mg/L at this time, and a high level of voriconazole is associated with neurotoxicity.

Thirdly, voriconazole is formulated as a sulfobutyl-ether cyclodextrin solution for intravenous administration which is renally cleared. Although CRRT effectively removes sulfobutyl-ether cyclodextrin and there is no significant accumulation [11], the use of voriconazole during renal insufficiency without CRRT is not recommended due to the lack of data.

Testing for plasma concentration of isavuconazole has not been routinely established yet. Although a relationship between dose-response and plasma concentration-response has been shown in animal models, limited data are available to define a target therapeutic range [12].

To evaluate the therapeutic efficacy of therapy, we performed quantitative GM testing in BAL regularly. The value decreased from ODI of 5.5 to 4.1 (day 20) to 1.7 (day 43). The literature points to a significant correlation between the decrease of GM and survival [3, 13]. Furthermore, negative GM tests 12 weeks after start of therapy predicts a good clinical outcome [13]. However, in the mentioned studies GM monitoring applies to serum samples. Serial testing from repeatedly performed BAL is not described in literature, thus no routinely established procedure. However, GM was negative in serum in our patients so we could not use it as monitoring tool, therefore we measured GM in BAL every time bronchoscopy was performed. There were different indications for bronchoscopy, most of the time desobliteration of impacted mucus or new sampling because of the clinical suspicion of a superinfection. However, due to the high risk of lung bleeding, we did not perform any further bronchoscopies after day 44. Regular follow-up CT scans demonstrated a decrease in size of fungal lesions at first, but later, they persisted in size.

Limited data are available concerning the duration of therapy for APA in patients without haematological disorders. The 2016 guidelines of the Infectious Diseases Society of America [3] recommend a duration of at least 6 to 12 weeks.

In this case, we could show adequate response to therapy with voriconazole and isavuconazole in the case of acute aspergillosis. However, medical treatment was not sufficient but surgical resection was deemed necessary.

Further, we showed the necessity of regular serum level testing due to altered metabolism in patients at the ICU. In septic shock our patient needed higher doses to receive adequate serum levels, after clinical improvement lower ones. The case also showed that regular therapeutic monitoring (imaging and GM testing) is essential. The decrease of GM value in BAL consistent with the clinical and radiographic improvement demonstrates that serial testing from repeatedly performed BAL might serve as monitoring tool in APA as well as serum. However, we want to highlight the lack of studies regarding this issue. Therefore, serial GM testing in BAL can just recommend if bronchoscopy has performed due to another reason (e.g., new sampling because of the clinical suspicion of a superinfection) until studies show the efficiency as a monitoring tool.

To sum up, aspergillosis is associated with high mortality rates. It is vital to take into account all the risk factors, especially influenza as a newly described one. Due to the difficult diagnosis and therapy, it is advisable to care for affected patients in a multidisciplinary team involving infectious disease specialists and thoracic surgeons. Further studies are urgently needed to deepen the understanding about the association between influenza and APA and to shed further light on the duration of antifungal therapy.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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