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Invasive pulmonary aspergillosis post extracorporeal membrane oxygenation support and literature review

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ABSTRACT

The use of extracorporeal membrane oxygenation (ECMO) for reversible pulmonary failure in critically ill patients has increased over the last few decades. Nosocomial infections are a major complication of ECMO and fungi have been found to be a common cause. Herein, we describe a case of invasive pulmonary aspergillosis following ECMO, which was successfully treated with combination antifungal therapy and interferon-gamma.

1. Introduction

The use of extracorporeal membrane oxygenation (ECMO) for intensive care patients with severe cardiac or reversible pulmonary failure has become more common over the last 30 years [1]. Complications resulting from ECMO further increase the mortality in this group of patients, which is already high due to severity of underlying illness [2]. After haemorrhage, infection is the second most common complication of ECMO, with reports of up to 45% of patients being affected [2,3]. Fungi such as *Candida* have been found to be a common cause of infection in this group [4]. We describe a case where ECMO was employed as a part of the management of severe community acquired pneumonia (CAP) and the patient developed an invasive pulmonary infection with *Aspergillus fumigatus*. This is the first case to describe successful treatment with combination antifungal therapy and interferon-gamma. This case report also highlights the difficulty in diagnosing invasive pulmonary aspergillosis (IPA), the importance of monitoring voriconazole levels in the blood and of careful consideration of antifungal drug interactions with other medication.

2. Case

A 48 year-old male presented with a 7-day history of cough, shortness of breath and diarrhoea. His past medical history included hypertension, chronic obstructive pulmonary disease (COPD) and diet-controlled diabetes. Furthermore, he had worked as a welder and was an ex-smoker. He was initially treated with amoxicillin and steroids by his general practitioner but after 4 days his symptoms worsened which led to hospital admission (day 0). He presented with severe sepsis. Blood tests showed an increase in the markers of infection (C-reactive protein and total white cell count were 279mg/L and 21.9×10^9/L respectively) and he had a base excess of -19.3. A chest radiograph revealed right-sided consolidation. A diagnosis of severe CAP was made and a course of intravenous amoxicillin-clavulanate and clarithromycin was started. Unfortunately, he rapidly developed multi-organ failure including type II respiratory failure and further deteriorated resulting in a peri-arrest situation. He was therefore intubated and transferred to the intensive care unit (ICU) where he received sustained low-efficiency dialysis (SLED). A computed tomography (CT) scan of his chest showed dense consolidation throughout his right lung, with cavitations in the right upper lobe (day +1). A bronchoalveolar lavage (BAL) grew *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Haemophilus influenza*. His antibiotic therapy was changed to a combination of piperacillin–tazobactam, linezolid and clindamycin. He was given two doses of intravenous immunoglobulin for suspected Panton Valentine Leukocidin *S. aureus* (later found to be negative). Other tests including blood cultures, respiratory viral PCR, culture and PCR for *Mycobacterium tuberculosis* on BAL samples, culture of CT-guided aspirate from lungs, atypical pneumonia serology screen, stool culture and *Legionella* antibody and urinary antigen were all negative. His condition worsened despite high frequency oscillatory

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ventilation and therefore he was referred for consideration of, and ultimately transferred for, ECMO at another tertiary centre (day +4). On day +22, he was transferred back to our ICU after his condition improved, but he remained critical. He had persistent pyrexia despite treatment with linezolid and ciprofloxacin, with fluconazole prophylaxis. A repeat CT scan of his chest revealed a large abscess in the right lung (Fig. 1). A CT scan of the head showed 1.5 cm lesions in the thalamus, basal ganglia and frontal lobe, which were thought to be either fungal infection or haemorrhage secondary to ECMO. *A. fumigatus* was grown from BAL and an endotracheal aspirate (ETA) and he was started on amphotericin B (amBisome) increasing to 5 mg/kg and other antibiotics were stopped (day +24).

A repeat BAL grew *Serratia marcescens* and *A. fumigatus* so he was restarted on piperacillin–tazobactam (day +31). A further ETA grew *S. aureus* therefore flucloxacillin, clindamycin, and rifampicin were added. Repeat BAL grew more *S. aureus* and *A. fumigates* (day +34). The patient remained pyrexial and unable to be weaned from ventilatory support. On day +37, a chest drain was inserted into the intra-pulmonary abscess under CT guidance. Cultures grew profuse *A. fumigatus* sensitive to posaconazole, itraconazole, voriconazole, amphotericin, and caspofungin. Voriconazole was added to amBisome (day +39) after a 2-week course of the latter due to the well recognised penetration of this agent into brain tissue. His liver function deteriorated, possibly due to an interaction between rifampicin and voriconazole. Moreover, concomitant rifampicin and voriconazole are contra-indicated as the former is known to reduce the exposure of voriconazole by more than 90% by inducing cytochrome P450 so rifampicin was stopped. A repeat ETA aspirate grew *Klebsiella oxytoca* and *Enterobacter cloacae* (day +58). Gentamicin was added and he had a further course of piperacillin–tazobactam. Aspergillus PCR on blood was negative but this does not preclude a diagnosis of invasive aspergillosis (day +60). Trans-oesophageal echocardiography was performed due to ongoing pyrexia and it ruled out endocarditis. Toxoplasma serology and HIV testing were carried out and both were negative. The patient was found to be anaemic, lymphopaenic, and thrombocythaemic (day +72). Investigations for immune compromise were carried out, particularly as the patient had been well prior to his admission, multiple organisms had grown on culture and disease had remained severe despite appropriate antifungals and antibiotics. A bone marrow aspirate showed no changes attributable to lymphoma however plasma B cells were abnormally low. His IgG was 22.20 g/L, which was appropriately elevated and compatible with infection. IgA was 6.73 g/L (moderately elevated) and IgM 0.80 g/L, which was normal. Lymphocyte subsets were normal apart from a low CD 19 (B cell) count of 15×106/L. A CT scan did not show changes suggestive of lymphoma. These investigations suggested functional immune impairment and the patient was not responding to treatment. After discussion with immunologists and a thorough literature search a course of interferon-gamma was initiated (day +82). After 3 weeks of voriconazole and 5 weeks of amBisome, ETAs were still yielding *A. fumigatus*. Following expert mycologist advice amBisome was discontinued, and the patient started anidulafungin (day +93) whilst continuing voriconazole. We aimed to have voriconazole levels more than 1 mg/L but less than 6 mg/L and the levels were regularly monitored. Low trough voriconazole levels of < 0.1 mg/L were found, probably due to the prior exposure to rifampicin, so we increased the dose from 200 mg b.d. to 300 mg b.d. After this, voriconazole levels remained around 1.8 mg/L. Mycology experts advised a minimum of 12 weeks of antifungal therapy. Following this, a CT chest and head revealed that abscesses and lesions were decreasing in size. Blood samples were taken and although serum *Aspergillus* galactomannan was not detected the β-1,3 glucan level was 115 pg/mL which was above the 80 pg/mL cut-off for positivity. Cardiothoracic surgeons reviewed the patient for consideration of pulmonary abscess excision, but they did not feel intervention was feasible. A particularly resistant *Enterobacter cloacae* grew from chest samples and antibiotics were changed to meropenem and then ciprofloxacin and he finished 6 weeks of flucloxacillin. Flucloxacillin was restarted for 2 weeks only a month later (day +118), and then again after another 2 weeks as *S. aureus* grew from blood cultures, peripherally inserted central catheter (PICC line) tip and sputum. He remained on anidulafungin and voriconazole and on day +150 in ICU CT imaging showed chest and brain lesions were further reducing in size. Anidulafungin was stopped after 4 months and the patient was switched to oral voriconazole after 5 months, with a plan to continue this for long-term maintenance along with flucloxacillin. He was discharged to the medical high dependency unit (MHDU) after +166 days on ICU. He was then transferred to a respiratory ward and made progress before transfer to a rehabilitation ward and then discharged home. Currently the patient has no chest symptoms or confusion, can walk with a stick but has some residual weakness. He remains on flucloxacillin 500 mg b.d and voriconazole 300 mg b.d.

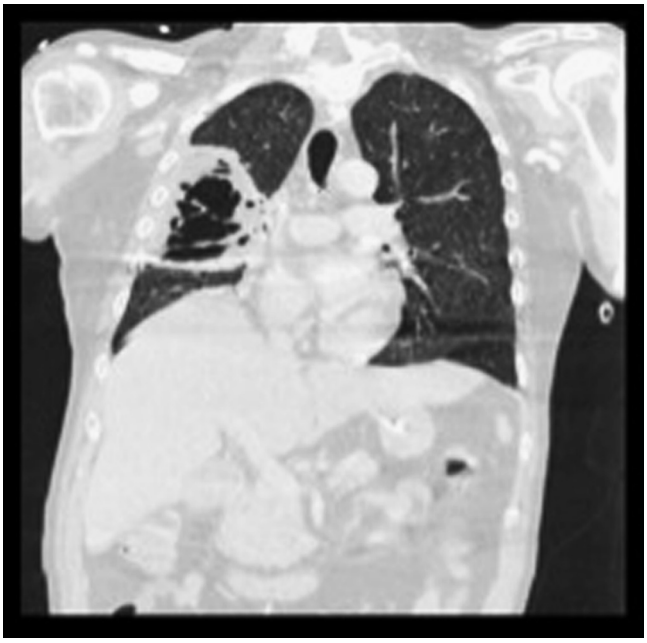

Fig. 1. CT chest scan showing large intrapulmonary collection posterolaterally in right upper lobe measuring up to 14.5 cm with multiloculated gas and fluid. There is collapse consolidation of basal right lower lobe.

3. Discussion

Aspergillus is a ubiquitous environmental hyaline mould. Typically, invasive aspergillosis affects patients who are immunocompromised such as patients with inherited immunodeficiencies, advanced HIV infection, prolonged neutropenia and allogeneic hematopoietic stem cell transplantation (HSCT) [5]. Aspergillosis is also an emerging opportunistic infection in critically ill patients in the ICU, particularly in patients with COPD or severe liver disease [6]. Over the last three decades the use of ECMO for the management of life threatening pulmonary or cardiac failure (or both) has increased. Prolonged ECMO use has been identified as a risk factor for ECMO-related nosocomial infection [2,7]. Patients are at risk of nosocomial infection whilst on ECMO as they have multiple portals of entry [2,8]. Fungi such as *Candida* have been identified as a common cause of infection in this group [4,9].