CASE REPORT

Sudden death in a patient with bone marrow transplant by a fungus among us

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SUMMARY

Mucormycosis is rare, presenting as breakthrough infection among haematological and transplant patients on prophylaxis with voriconazole. We report an unusual presentation of this infection, that which is pneumonia progressing to cardiac arrest. A 68-year-old woman with refractory acute myelogenous leukaemia on voriconazole prophylaxis was initially admitted for neutropenic fever and pneumonia. She was discharged improved on antibiotics and voriconazole for presumed aspergillosis. She returned after 1 month with the same presentation. She eventually improved on antibiotics and voriconazole, and eventually received bone marrow transplantation. Three days later, she developed pleuritic chest pain, dyspnoea, and hypoxia requiring intubation. An hour after intubation, the patient arrested and expired. Autopsy revealed *Rhizopus* pneumonitis with pulmonary infarction, and emboli to her cerebellum, heart, thyroid and kidney. Mucormycosis is an emerging, fatal infection that should be suspected in haematological and transplant patients who deteriorate on voriconazole.

BACKGROUND

Mucormycosis is an emerging, fatal fungal infection afflicting severely immunocompromised patients. Recently, an increasing incidence of mucormycosis has been observed among patients with haematological malignancies and haematopoietic stem cell transplantation (HSCT) recipients. The introduction and widespread use of voriconazole prophylaxis, an agent with no activity against mucormycosis in these patients is thought to be associated with this trend, but remains controversial. Despite the high mortality associated with mucormycosis, its diagnosis remains challenging, consequently delaying the institution of appropriate antifungal treatment. We aim to summarise the current state of knowledge about the epidemiology, risk factors, and diagnosis of mucormycosis in patients with HSCT.

CASE PRESENTATION

A 68-year-old woman with refractory acute myelogenous leukaemia on voriconazole prophylaxis was previously admitted for neutropenic fever and multifocal pneumonia suggestive of a fungal aetiology on chest CT (figure 1). She was discharged improved on antibiotics and treatment dose voriconazole for presumed invasive aspergillosis. At this point, no bronchoscopy was performed. One month later, she was admitted for fever and dyspnoea with a new left lower lobe consolidation on chest CT. Levofloxacin was prescribed and voriconazole was continued.

Figure 1 Multifocal pneumonia, with some of the consolidations appearing nodular, suggestive of fungal aetiology.

After 3 weeks, the patient clinically improved and was cleared for bone marrow transplantation. Her pretransplant chest CT showed slight improvement of her left lower lobe infiltrates. Three days post-transplant, however, patient reported right hand tremor and weakness, and new left pleuritic chest pain followed by sudden onset of respiratory distress and hypoxia requiring intubation. Chest X-ray showed worsening bilateral infiltrates. An hour after intubation, the patient arrested and expired. Autopsy revealed *Rhizopus* spp (figure 2) pneumonitis with invasion of pulmonary arteries and veins resulting in a large pulmonary infarct in the left upper lobe. Multiple fungal emboli were also noted in the heart apex, thyroid, right kidney, and a haemorrhagic infarction of the right cerebellar hemisphere.

Figure 2 Histopathological examination of tissue showing the broad-septate hyphae of *Rhizopus* spp. *Rhizopus* was found in the patient's lung, heart, thyroid, spleen and brain.

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INVESTIGATIONS

See [figure 1](#) for chest CT scan.

DIFFERENTIAL DIAGNOSIS

- ▶ Bacterial pneumonia
- ▶ Pulmonary embolism
- ▶ Septic embolism
- ▶ Invasive aspergillosis
- ▶ Disseminated mucormycosis

DISCUSSION

Mucormycosis refers to a group of filamentous fungi in the order Mucorales, class Zygomycetes.¹ These organisms are ubiquitous in nature, and can be found in soil or decaying organic matter.² Mucormycosis can cause severe and fatal infections in humans, especially in immunocompromised patients.³ *Rhizopus*, *Rhizomucor*, *Mucor* and *Absidia* are the most common genera implicated in human infections.⁴ Angiotropism or the ability to invade blood vessels leading to thrombosis and tissue necrosis is a unique and important feature of this fungal infection.⁵

There has been increased incidence of mucormycosis in patients with haematological malignancies and HSCT recipients in the past 30 years.⁶ Coincidentally, this trend has been observed with the introduction and widespread use of voriconazole, an antifungal with no clinically useful activity against mucormycosis as prophylaxis in the setting of HSCT. This has brought into question whether an epidemiological link between voriconazole use and mucormycosis exists.

In patients with haematological malignancies and HSCT recipients, mucormycosis has emerged as the third most common invasive mycosis after candidiasis and aspergillosis.¹ The Transplant Associated Infections Surveillance Network reported that mucormycosis accounted for 8% of invasive fungal infections.⁷ In the past decade, single institutions have reported an increased incidence of mucormycosis in patients with HSCT.^{8–11} Data of the University of Texas M.D. Anderson Cancer Center showed an increased incidence of mucormycosis among patients with HSCT from 0.25% during 1989–1998 to 1.55% during 2002–2004.⁷ Although the number of cases of mucormycosis in these studies is low, its occurrence appears to be rising.

Mucormycosis occurs almost exclusively in patients who are immunocompromised. The risk of mucormycosis is highest in patients with haematological malignancies, especially those undergoing allogeneic HSCT,¹² and those with poorly controlled diabetes mellitus.³ Other important conditions predisposing to mucormycosis include prolonged and severe neutropenia, iron overload, and prolonged use of corticosteroids.^{13 14}

Several studies have reported an association between prior voriconazole exposure, and the development of mucormycosis in patients with HSCT. A small retrospective study by Trifilio *et al*¹⁵ reported that 40% of patients diagnosed with mucormycosis received voriconazole prophylaxis. A single-institution prospective study involving 27 patients reported voriconazole prophylaxis as an independent risk factor (OR 10.37 (95% {CI} 2.76 to 38.97); $p=0.001$), for developing mucormycosis in patients with haematological malignancies and HSCT recipients.⁸ These findings are in contrast to those of a large, randomised controlled trial, which showed no difference in the occurrence of mucormycosis in patients with HSCT who received either fluconazole or voriconazole prophylaxis (2 of 295 patients in the fluconazole group vs 3 of 305 patients in the voriconazole group). However,

the overall incidence of invasive fungal infections in this study was low; hence, a true difference could not be detected.¹⁶

At present, it remains unclear whether there is a causal link between the occurrence of mucormycosis and voriconazole use in patients with HSCT, and further prospective studies are warranted to examine this association. More importantly, the exact mechanism on how voriconazole acts as a risk factor for mucormycosis has not been fully elucidated. One hypothesis is that voriconazole promotes virulence of mucormycosis. Preclinical studies using animal models demonstrated that exposure of *Rhizopus oryzae* to voriconazole enhanced its the growth and virulence, and resulted to worse survival of infected animals.¹⁷

Tissue-based diagnosis is the gold standard for diagnosis of mucormycosis.¹⁸ A histopathological proof of mycelia in tissue, with or without a positive culture is required for definitive diagnosis.¹⁹ However, establishing a definite diagnosis with biopsy is hampered because patients with haematological malignancies and HSCT recipients are often thrombocytopenic or haemodynamically unstable.¹⁸

In addition, standard fungal culture lacks sensitivity and specificity. Two-thirds of histopathologically proven mucormycosis are culture negative.¹⁹ Furthermore, false-positive culture results frequently occur because of contamination of samples obtained from non-sterile sites (eg, sputum) and other laboratory contaminants.¹⁸ Non-culture-based diagnostic methods for mucormycosis, such as PCR remain investigational.¹⁹

The prognosis of patients with mucormycosis is poor, with a mortality rate ranging from 50% to 70%, and as high as 95% with extrathoracic dissemination.^{6 18} Amphotericin B is considered the mainstay therapy, and if administered early, can result in better patient outcomes. If treatment is delayed, proliferation and dissemination of angioinvasive *Mucor* spp will result in thrombotic necrosis of tissues, thus limiting adequate delivery of antifungal agents to the sites of infection.¹⁹

Chamilos *et al* illustrated that delayed amphotericin B-based therapy (by >5 days after symptom onset) was associated with a twofold increase in the mortality rate at 4 weeks (35.1% vs 66.6%; $p=0.006$) and 12 weeks (48.6% vs 82.9%; $p=0.03$) after diagnosis, compared with early treatment. Once the infection has stabilised, posaconazole, an orally administered antifungal agent with activity against mucormycosis may be considered.¹⁹

Mucormycosis is a rapidly fatal fungal infection that usually affects immunocompromised patients, especially those undergoing HSCT. The increasing incidence of mucormycosis, and its possible association with voriconazole prophylaxis warrant larger prospective studies. Nevertheless, it is important to have a high clinical suspicion of mucormycosis in patients who deteriorate on voriconazole, an agent that lacks activity against mucormycosis. More importantly, more advanced laboratory techniques, such as molecular and antigen detection tests need to be developed to aid in the early diagnosis of mucormycosis, so that appropriate and timely treatment can be instituted to avert this devastating infection.

Learning points

- ▶ Mucormycosis can occur as a breakthrough infection in immunocompromised patients on voriconazole.
- ▶ It can present in many ways. Rarely, it can cause acute respiratory failure and sudden cardiac death, mimicking many acute processes, such as pulmonary embolism.
- ▶ Early recognition is important so that prompt treatment can be initiated in a timely manner.

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