CASE REPORT

Rapidly progressing dual infection with *Aspergillus* and *Rhizopus*: when soil inhabitants become deadly invaders

Milind Bhagat,¹ Alwyn Rapose²

¹Department of Internal Medicine, Saint Vincent Hospital, Worcester, Massachusetts, USA
²Department of Infectious Diseases, Reliant Medical Group and Saint Vincent Hospital, Shrewsbury, Massachusetts, USA

Correspondence to
 Dr Alwyn Rapose,
 alwyn.rapose@gmail.com

Accepted 23 November 2016

SUMMARY

We present a case report of a 61-year-old patient with acute pulmonary and cerebral infections with *Aspergillus* and *Rhizopus*. The only risk factor for invasive fungal disease was high-dose corticosteroids used to treat her chronic obstructive pulmonary disease exacerbation. She had rapid progression and succumbed to her infections within 2 weeks of diagnosis in spite of aggressive antifungal therapy and surgery. To the best of our knowledge, this is the first reported case of rapidly fatal dual infection with *Aspergillus* and *Rhizopus*. Our case highlights the role of high-dose corticosteroids as a risk factor for invasive fungal disease in patients without traditional risk factors like haematological malignancies, solid organ transplantation or uncontrolled diabetes.

BACKGROUND

Invasive aspergillosis is most often seen in the setting of prolonged neutropaenia, haematological malignancies and immunosuppression following solid organ transplantation.¹ Pulmonary aspergillosis is seen most commonly in patients with lung transplantation, but is now being seen more frequently in patients with chronic obstructive pulmonary disease (COPD) on long-term corticosteroid therapy.² Infection of the central nervous system (CNS) is associated with the highest mortality among all forms of *Aspergillus* infections.¹

Pulmonary and CNS *Rhizopus* infection on the other hand is less common. *Rhinocerebral mucormycosis* is the most commonly recognised form of this infection and is associated with diabetic ketoacidosis.³ It is considered the most aggressive mould infection of the CNS and carries a very high mortality risk.⁴

Patients with severe exacerbations of COPD need high-dose corticosteroids which place them at increased risk for invasive fungal diseases. Our case report highlights the need to be vigilant for these infections in patients on high-dose corticosteroids.

Aspergillus and *Rhizopus* infections carry a very poor prognosis if there is pulmonary and cerebral involvement.

CASE PRESENTATION

A 61-year-old Caucasian woman was admitted to hospital with a 3-week history of progressive shortness of breath and non-productive cough. She had been recently treated twice as an outpatient for the same symptoms, each time with a 1-week tapering course of prednisone along with an antibiotic. Her

medical history was significant for non-oxygen-dependent COPD with previous flare-up 2½ months back. She had quit smoking 14 years ago after a 70-pack-year smoking history. Physical examination revealed temperature of 98.2°F (37°C), heart rate 110 bpm, respiratory rate 24 breaths per minute, oxygen saturation 92–94% on 4 L oxygen by nasal cannula. Auscultation of the chest revealed bilateral expiratory wheeze.

INVESTIGATIONS

Laboratory workup revealed an elevated leucocyte count ($23.1 \times 10^9/L$). Chest X-ray revealed trace bilateral pleural effusions, but no focal consolidation. A CT scan revealed tree-in-bud nodularity representing viral inflammation or infection, but no consolidation, and no pulmonary embolism (figure 1A, B).

Figure 1 Initial CT scan (A) showing the lung bases, (B) showing mid-lung region.

CrossMark

To cite: Bhagat M, Rapose A. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217535

DIFFERENTIAL DIAGNOSIS

COPD exacerbation, viral pneumonia.

TREATMENT

The patient was initially started on oral prednisone 60 mg once a day. However, she experienced acute decompensation with oxygen desaturation to 81% on 6 L oxygen by nasal cannula. She was given non-invasive positive pressure ventilation, and transferred to the intensive care unit (ICU). She was switched to intravenous methylprednisolone 60 mg every 8 hours. Infectious diseases specialty was consulted and a decision was made to withhold antibiotics as she had recently completed a 10-day course of doxycycline, followed by a 7-day course of levofloxacin as outpatient.

OUTCOME AND FOLLOW-UP

In the ICU, the patient improved and intravenous steroids were gradually tapered down to 60 mg once a day over the next 8 days. Blood cultures obtained on admission were negative. HIV test, urine *Legionella* antigen and serum *Mycoplasma* antibody were all negative. However, on day 12, she developed acute shortness of breath, wheezing and high oxygen requirements. A sputum sample revealed respiratory flora. Her intravenous steroids were increased. Once again she appeared to improve. Throughout this time, she remained afebrile. On day 15, the patient experienced episodes of streaky haemoptysis. Sputum cultures revealed *Aspergillus* species. An urgent chest CT scan was obtained. It revealed abscesses in bilateral lower

lobes, multiple bilateral pulmonary nodules some with central cavitation and air-fluid levels (figure 2A, B). Infectious diseases was consulted again and their recommendations were to obtain blood cultures, bronchoscopy with bronchoalveolar lavage (BAL) for pathology and cultures, and initiation of broad parenteral antimicrobial coverage with vancomycin, meropenem and voriconazole. Multiple sets of blood cultures were negative. A bronchoscopy was performed. Smear from BAL revealed fungal elements consistent with *Aspergillus* species (figure 3A, B). Cultures for bacteria and mycobacteria were negative. Unfortunately over the next 48 hours, the patient became increasingly dyspnoeic, drowsy, developed facial asymmetry and required intubation and mechanical ventilation. A CT scan of the head revealed a 6 cm ring-like mass with surrounding oedema involving the right thalamic nuclei and brainstem (figure 4A–C). Intravenous micafungin was added to her regimen. Vancomycin and meropenem were discontinued when bacterial cultures were confirmed negative. Corticosteroids were reduced. Neurosurgery was consulted and MRI was obtained. MRI revealed a heterogeneous peripherally enhancing partially necrotic mass with surrounding oedema (figure 5A–C) extending into the midbrain and pons, with obstructive hydrocephalus secondary to mass effect on the third ventricle. It also revealed a 7.1 mm midline shift to the left and subfalcine herniation. The patient underwent a right craniotomy with evacuation of abscess, and placement of ventriculostomy. Postoperatively she was initiated on intrathecal amphotericin B. Intravenous voriconazole as well as micafungin were continued. Unfortunately she continued deteriorating and ultimately succumbed to her infection. An autopsy was declined by the family. BAL cultures grew *Aspergillus fumigatus* as well as *Rhizopus* species. Brain tissue was also positive for fungal elements identified later as *Aspergillus* and *Rhizopus*.

DISCUSSION

Aspergillus and *Rhizopus* species are soil inhabitants. The port of entry in human infection is the respiratory tract by the inhalation of spores. Development of invasive disease depends on the inoculating dose, host immunity and virulence of the organism.^{5 6} Sputum or tissue from patients with invasive *Aspergillus* infection reveal narrow (2–5 micron diameter) septate hyphae branching at 45° angles. *A. fumigatus* accounts for ~90% of human *Aspergillus* infections. Invasive aspergillosis almost always occurs in patients with seriously compromised immune system like patients with haematological malignancies, transplant recipients or congenital immunodeficiency.¹ However, there have been increasing reports of cases of invasive pulmonary aspergillosis (IPA) in patients with COPD on corticosteroids as well as patients in the ICU without any of the above risk factors.^{5 7–10} Steroids enhance the growth of *Aspergillus*, decrease macrophage antifungal activity, inhibit neutrophils activity and suppress T helper cell type 1 cytokine.⁵ It still remains unclear why some patients are only colonised with *Aspergillus* while others develop invasive disease.^{2 11} Finding *Aspergillus* in sputum has poor predictive value for diagnosing the invasive disease and bronchoscopy is necessary for early diagnosis when an invasive disease is suspected clinically.¹² *Aspergillus* CNS infection carries a poor prognosis and is associated with significantly high mortality.¹

CNS and pulmonary mucormycosis are very aggressive human fungal infections and carry a very high mortality risk.⁴ It is most commonly associated with diabetic ketoacidosis.³ *Rhizopus* is the most common genus associated with mucormycosis.¹³ Tissues invaded by *Rhizopus* reveal broad (5–15 µ

Figure 2 CT scan on day 15 (A) lung bases with cavitory consolidations, (B) mid-lung with cavitory nodule.

Figure 3 H&E stain of bronchoalveolar lavage showing fungal elements with branching septate hyphae consistent with *Aspergillus* species (A) $\times 10$, (B) $\times 40$.

diameter), non-septate hyphae branching at 90° angles. There are clear differences in the hyphae between *Aspergillus* and *Rhizopus* and this allows presumptive identification in clinical specimens. *Rhizopus* is a ubiquitous fungi causing fatal disease in patients with malignant haematological disorders, organ or bone marrow transplant, deferoxamine therapy in patients receiving haemodialysis, uncontrolled diabetes mellitus, neutropaenia and patients receiving glucocorticoid therapy.⁶

Pulmonary *Rhizopus* infection is less common than CNS infection and culture for speciation is difficult.^{14 15} However,

some case series have reported as high as 71% cases of pulmonary involvement.¹⁶

Early recognition based on high clinical suspicion is very essential to improve survival in *Aspergillus* and *Rhizopus* infections. The Infectious Diseases Society of America has published comprehensive guidelines for diagnosis and management of invasive aspergillosis.¹ These included strong recommendations for bronchoscopy and BAL to obtain appropriate clinical specimens for cytology, culture and histopathology. The Society also strongly recommended CT scan to help with early diagnosis based on high-quality evidence. While the classically described 'halo sign' (nodular consolidation with surrounding attenuation) represents angioinvasion associated with *Aspergillus* infection,¹⁷ patchy infiltrates and multiple nodules along bronchovascular bundles were seen more commonly in critically ill patients with COPD in one study.¹⁸ In contrast, 'reversed halo sign' where a focal ground-glass attenuation is seen surrounded by a halo of consolidation has been described in pulmonary mucormycosis especially in the setting of patients with neutropaenia.¹⁹

For a long time, amphotericin-B was considered as the mainstay of therapy for invasive fungal disease. However, voriconazole is now the first-line treatment for invasive *Aspergillus* infections.^{1 20} Several new drugs including the class of echinocandins have also been studied and the possibility of combination therapy have prospects of improving mortality rate for invasive *Aspergillus* infections.¹

On the other hand, management of cerebral *Rhizopus* infection involves aggressive surgery along with antifungals and prognosis remains poor.^{3 4 21} There are no randomised trials to compare the efficacy of different antifungal agents. Amphotericin B is considered the drug of choice, while the azoles and echinocandins are not effective against *Rhizopus*. Unfortunately for our patient, the culture results indicating *Rhizopus* infection were available only after she succumbed to her illness.

Our 61-year-old patient with COPD developed IPA and invasive *Rhizopus* infection within a short period of time while she was in hospital. Her initial sputum culture and chest CT scan had revealed no evidence to suspect invasive disease at the time of admission. Unfortunately, she required high doses of systemic glucocorticoids for control of her COPD exacerbations, and this was her only risk factor for invasive fungal disease. She developed aggressive infections with two invasive fungi, both invading her lungs and CNS, which resulted in her succumbing to her infection.

We have reviewed the medical literature, and to the best of our knowledge, this is the first case of dual infection with *Aspergillus* and *Rhizopus* in a patient with COPD.

Figure 4 CT scan of head showing large parenchymal mass (A) axial section, (B) coronal section, (C) sagittal section.

Figure 5 MRI of head showing necrotic mass (A) T2 axial, (B) T1 with gadolinium (C) MPGR (MultiPlanar Gradient Recalled acquisition in the steady state).

Learning points

- ▶ *Aspergillus* and *Rhizopus* are saprophytic fungi which cause fatal infections in immunocompromised patients.
- ▶ *Aspergillus* can be treated with systemic antifungals, but *Rhizopus* infections require aggressive surgical intervention.
- ▶ Systemic corticosteroids used for treatment of chronic obstructive pulmonary disease exacerbations are a risk factor for development of invasive fungal diseases.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Patterson TF, Thompson GR, Denning DW, *et al.* Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;63:e1–e60.
- 2 Barberán J, Candel F, Arribi A. How should we approach *Aspergillus* in lung secretions of patients with COPD? *Rev Esp Quimioter* 2016;29:175–82.
- 3 Roden MM, Zaoutis TE, Buchanan WL, *et al.* Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41:634–53.
- 4 McCarthy M, Rosengart A, Schuetz AN, *et al.* Mold infections of the central nervous system. *N Engl J Med* 2014;371:150–60.
- 5 Meersseman W, Vandecasteele SJ, Wilmer A, *et al.* Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med* 2004;170:621–5.
- 6 Petrikos G, Skiada A, Lortholary O, *et al.* Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis* 2012;54(Suppl 1):S23–34.
- 7 Rello J, Esandi M, Mariscal D, *et al.* Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: report of eight cases and review. *Clin Infect Dis* 1998;26:1473–5.
- 8 Muquim A, Dial S, Menzies D. Invasive aspergillosis in patients with chronic obstructive pulmonary diseases. *Can Respir J* 2005;12:199–204.
- 9 Ader F, Nseir S, Le Berre R, *et al.* Invasive pulmonary aspergillosis in chronic obstructive pulmonary disease: an emerging fungal pathogen. *Clin Microbiol Infect* 2005;11:427–9.
- 10 Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007;30:782–800.
- 11 Hope W, Walsh T, Denning D. The invasive and saprophytic syndromes due to *Aspergillus* spp. *Med Mycol* 2005;43(Suppl 1):S207–38.
- 12 Garnacho-Montero J, Amaya-Villar R, Ortiz-Leyba C, *et al.* Isolation of *Aspergillus* spp. from the respiratory tract in critically ill patients: risk factors, clinical presentation and outcome. *F Crit Care* 2005;9:R191–9.
- 13 Ibrahim A, Spellberg B, Walsh T, *et al.* Pathogenesis of mucormycosis. *Clin Infect Dis* 2012;54(Suppl 1):S16–22.
- 14 Tsykrunou AV, Ellison RT, Akalin A, *et al.* Multifocal *Rhizopus* microsporus lung infection following brush clearing. *Med Mycol Case Rep* 2014;6:14–17.
- 15 Severo L, Oliveira F, Dreher R, *et al.* Zygomycosis: a report of eleven cases and a review of the Brazilian literature. *Rev Iberoam Micol* 2002;19:52–6.
- 16 Kontoyiannis DP, Wessel VC, Bodey GP, *et al.* Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis* 2000;30:851–6.
- 17 Caillot D, Casasnovas O, Bernard A, *et al.* Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997;15:139–47.
- 18 Huang L, He H, Ding Y, *et al.* Values of radiological examinations for the diagnosis and prognosis of invasive bronchial-pulmonary aspergillosis in critically ill patients with chronic obstructive pulmonary diseases. *Clin Respir J* 2016;doi:10.1111/crj.12551.
- 19 Legouge C, Caillot D, Chrétien ML, *et al.* The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? *Clin Infect Dis* 2014;58:672–8.
- 20 Herbrecht R, Denning DW, Patterson TF, *et al.* Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408–15.
- 21 Riley TT, Muzny CA, Swiatlo E, *et al.* Breaking the mold: a review of mucormycosis and current pharmacological treatment options. *Ann Pharmacother* 2016;50:747–57.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow