CASE REPORT

Primary gut aspergillosis in a patient with acute myeloid leukaemia: the importance of early suspicion and definitive treatment

Elizabeth Li,¹ Hayder Hussein,² Adil Todiwala,² Robert Kirby¹

¹Department of General Surgery, University Hospital of North Staffordshire, Stoke-on-Trent, UK

²Department of Haematology, University Hospital of North Staffordshire, Stoke-on-Trent, UK

Correspondence to

Elizabeth Li,
yan.elizabeth.li@gmail.com

Accepted 9 February 2014

SUMMARY

Aspergillus infection is a known complication in immunocompromised patients, particularly in those with impaired neutrophil function. The pathophysiology of respiratory tract infection and disseminated disease are well understood, and guidelines exist for early detection and treatment. The gut has been speculated to be the potential portal of entry for *Aspergillus*, though previous case series outline that this is often discovered late and results in high morbidity and mortality. Early clinical suspicion, with definitive surgical intervention and antifungal treatment with voriconazole, can significantly increase the chances of survival. In this article, the authors discuss a case of primary gut aspergillosis with secondary dissemination in a patient with acute myeloid leukaemia who developed serious sequelae.

BACKGROUND

Fungal infections are a well-described complication in immunocompromised patients, particularly those with neutropenia or impaired neutrophil function. International guidelines recommend maintaining a high index of suspicion in patients with febrile neutropenia that is failing to resolve, with prompt investigation and empirical treatment.^{1 2} Fungal infections typically affect the upper and lower respiratory tracts, in the case of *Aspergillus* infection, and the liver and spleen, in the case of candidiasis. Invasive infections can lead to secondary dissemination to virtually all other organs, including the central nervous system (CNS).

Aspergillosis of the gut has been reported in association with disseminated fungal disease, and more rarely as a primary event.³ The associated mortality rate has been quoted at 47–60%, with significant rates of morbidity. It is thought that this relates to late diagnosis and treatment, as well as the severity of the underlying pathological process.

We report a case of primary gut aspergillosis and its associated complications in a patient with newly diagnosed acute myeloid leukaemia.

CASE PRESENTATION

A 63-year-old previously healthy man presented with persistent fevers, weight loss and fatigue. His initial blood tests showed pancytopenia and absolute neutropenia, with blasts seen on the peripheral smear. He was admitted to the haematology unit and was initiated on piperacillin-tazobactam as empirical treatment for febrile neutropenia. A subsequent bone marrow aspirate and trephine biopsy

confirmed a diagnosis of acute myeloid leukaemia without maturation, and cytogenetics confirmed the presence of trisomies 8 and 21.

Following a week of antibiotics, the patient developed diarrhoea, with no pathogenic organisms on culture. Tests for *Clostridium difficile* toxin were negative. As the patient's pyrexia persisted, a high resolution CT of the chest and a CT of the paranasal sinuses were performed, which showed no evidence of invasive fungal infection. A CT of the abdomen showed features suggestive of a pancolitis (not shown), which was thought to be due to severe neutropenia. Blood cultures had subsequently grown *Enterococcus faecalis*, which was treated with intravenous vancomycin. Serum galactomannan assays were not performed, as the test was not available at this centre.

Despite the antibacterial therapy, the patient's C reactive protein (CRP) remained elevated and fever continued. He remained clinically stable, and as his blast count was increasing, it was decided to start treatment with chemotherapy. He was enrolled onto the AML17 Trial and randomised for induction with Daunorubicin and Cytarabine.

Approximately 1 week after starting chemotherapy, the patient developed abdominal distension, vomiting and constipation. Paralytic ileus secondary to electrolyte loss and gut inflammation was initially suspected, and an abdominal X-ray confirmed dilated loops of the small bowel. A CT of the abdomen subsequently showed mechanical obstruction, thought to be due to intussusception (figure 1). Following surgical review, a trial of conservative management was recommended, with the hope of full blood count recovery prior to proceeding to surgery.

Figure 1 CT of the abdomen contrast-enhanced image showing small bowel mass and dilation.

CrossMark

To cite: Li E, Hussein H, Todiwala A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202316

Figure 2 Macroscopic appearance of resected small bowel aspergilloma.

TREATMENT

As there was no improvement after 5 days, and the risk of perforation was deemed to be unacceptably high, the patient underwent surgery. The procedure was supported with platelet and red cell transfusions, and intravenous meropenem and vancomycin cover. A small bowel mass, adjacent to the sigmoid colon, was identified and excised (figure 2). This was followed by a primary small bowel anastomosis and formation of a double-barrelled sigmoid colostomy.

The patient had no fever following surgery and initially made good progress. His full blood count recovered, suggesting that a significant remission was obtained from his leukaemia. Unfortunately, 5 days postoperatively, he again had fever and developed a sudden onset of dense right sided weakness, occipital blindness and dysphagia. A CT of the brain with CT arteriography showed ischaemic changes in territories that were discordant with the patient's neurological signs, though with no evidence of a thrombus. An MRI showed multifocal infarcts in all cerebral territories (figure 3). The patient was started on aspirin and transferred to the acute stroke unit for intensive rehabilitation. The patient had no risk factors for a stroke; investigations showed that the patient was in sinus rhythm; an echocardiogram showed no evidence of intracardiac thrombus, and carotid Dopplers showed no significant stenosis.

Histology of the small bowel resection showed fungal hyphae consistent with *Aspergillus* species (figure 4). The sections revealed invasion of the blood vessels, with heavy growth. It was thought that the patient's multifocal stroke was caused by

secondary dissemination of primary gut aspergillosis, and treatment was started with intravenous voriconazole to achieve CNS penetrance and fungicidal activity.

OUTCOME AND FOLLOW-UP

The patient is now 4 months post his initial diagnosis of leukaemia and remains in remission. He has a residual Medical Research Council (MRC) Scale grade 4 arm weakness and a mild visual field defect, but is otherwise independent and self-caring. He continues on oral voriconazole with a view to maintain this for at least 6 months. A post-treatment bone marrow shows he is in complete remission from his acute myeloid leukaemia. Following a detailed discussion about the high risk of leukaemia relapse against the risk of worsening fungal infection, the patient decided to proceed with consolidation chemotherapy with an intermediate dose of cytarabine, which he has been receiving at the time of writing.

DISCUSSION

Invasive aspergillosis is a well-recognised cause of morbidity and mortality in immunocompromised patients. The most commonly recognised presentation is associated with primary lung disease, with persistent fever, pleuritic chest pain and haemoptysis. Sinus disease typically manifests again with persistent fever and localised symptoms of congestion or pain. Without recognition and treatment, *Aspergillus* infection progresses relentlessly and is universally fatal. As well as direct extension and invasion of adjoining structures, haematogenous dissemination can also occur, including to the CNS. The diagnosis of CNS disease requires a high degree of clinical suspicion, due to the lack of consistent presentation. Features can include focal neurological deficits, discordant cranial nerve palsies or more global effects, such as a change in the mental state or seizures.

Guidelines for diagnosis of fungal infections in neutropenic patients have focused on imaging of the chest and sinuses, bronchoalveolar lavage and testing for galactomannan antigenaemia.^{1 2} In the context of a patient with persisting fever, the diagnostic yield of these tests would be expected to be sufficient to detect infection. The galactomannan antigen is a polysaccharide present in the cell wall of *Aspergillus* species and can be detected in serum, cerebrospinal fluid and bronchoalveolar lavage fluid in infected patients. Though it can be associated with a false positive rate, its clinical utility as an adjunct to diagnosis has been endorsed in several clinical guidelines. However, despite the assay being available for over 10 years, its use is not routine in many UK and European centres. This is perhaps due

Figure 3 T1 (left) and T2 (right) weighted brain MRI showing multifocal infarcts in all territories (arrowed).

Figure 4 Microscopic appearance of bowel specimen, histology showing *Aspergillus* hyphae (periodic acid Schiff stain and Grocott stain).

to the perceived efficacy of empirical antifungal treatments and the improved sensitivity of imaging as a modality for diagnosis.

Secondary dissemination of invasive fungal infection to the gut from other sites has been quoted at 4% in previous case series.³ The incidence of the gut as a portal of entry for *Aspergillus* infection is rare, with a reported incidence of approximately 1% of cases of fungal infection.³ This is thought to be an underestimate, due to the higher rates found in autopsy series.⁴ Diagnostic difficulty has been highlighted as a recurring theme in previous case series.^{3 5} The presentation of intra-abdominal fungal disease ranges from severe diarrhoea to frank peritonitis, with perforation and haemorrhage, to obstruction. As the presentation can be similar to neutropenic enterocolitis, such as in this case, treatment is often directed with antibacterials. This can be reinforced by the presence of positive blood cultures for gut organisms, in this case *Enterococcus* species.

This case illustrates several time points where early treatment with antifungal treatment may have been started. Although there was an identified source of infection in the form of colitis, and conventional screening with lung and sinus imaging was clear, the persisting pyrexia was a firm indication for starting

therapy with antifungal agents.^{1 2} Second, the presence of an obstructive lesion both at the time of imaging and at surgery should alert the clinicians to the possibility of a fungal lesion. The rarity of the presentation meant that these findings were not recognised. The authors speculate that these delays may have led to the secondary dissemination of the infection, with spread to the CNS.

Despite the significant morbidity that this patient endured, he responded to surgical excision of the lesion and ongoing therapy with voriconazole. At the time of writing, he is independent with mild neurological deficits. However, the challenge that currently faces him is proceeding with further antileukaemia treatment and the risk of worsening fungal infection.

Acknowledgements The authors would like to acknowledge the contributions of Dr S Pillai, Consultant Haematologist University Hospital of North Staffordshire, who had direct care of the patient and also revised the paper; and Dr B Latifaj, Consultant Pathologist University Hospital of North Staffordshire, who provided the specimen images and guidance in interpretation.

Contributors EL, HH, AT and RK were involved in the clinical care of the patient. Each contributed towards the collection of relevant data and images, drafting of the manuscript and revision of the paper.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Aspergillosis of the gut is a rare complication of prolonged neutropenia.
- ▶ Empirical treatment with antifungals is warranted in at-risk patients with persisting fevers and gastrointestinal (GI) symptoms, even in the absence of fungal infection elsewhere.
- ▶ Recurrent positive blood cultures with gut organisms should not distract the clinician from the possibility of superadded fungal infection.
- ▶ Surgical treatment reduces the fungal burden and is feasible in patients with pancytopenia.

REFERENCES

- 1 Walsh TJ, Anaissie EJ, Denning DW, *et al.* IDSA guidelines treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:327–60.
- 2 Maertens J, Marchetti O, Herbrecht R, *et al.* European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 Update. *Bone Marrow Transplant* 2011;46:709–18.
- 3 Eggiman P, Chevrolet M, Starobinski M, *et al.* Primary invasive aspergillosis of the digestive tract: report of two cases and review of the literature. *Infection* 2006;34:333–8.
- 4 Hori A, Kami M, Kishi Y, *et al.* Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. *J Hosp Infect* 2002;50:175–82.
- 5 Kazan J, Maertens R, Herbrecht R, *et al.* A retrospective series of gut aspergillosis in haematology patients. *Clin Microbiol Infect* 2011;17:588–94.

Copyright 2014 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