Fungal diseases at the medical front door

ABSTRACT

Fungal diseases are an increasingly recognized cause of mortality worldwide and often pose diagnostic challenges. This article focuses on common fungal diseases as they may present in the acute medical unit, looking at the initial investigation and management of four common diseases: *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, candidaemia and allergic bronchopulmonary aspergillosis. There is an increase in morbidity and mortality if these conditions are not correctly diagnosed and thus appropriate therapy is delayed. A better understanding of the initial investigation and management of these conditions will improve the outcome of patients with fungal diseases presenting to the 'medical front door'.

Having previously been regarded as uncommon, fungal diseases are an increasingly recognized common cause of morbidity and mortality worldwide (Brown et al, 2012, 2014). They often pose diagnostic challenges, and investigation and management of fungal diseases can be complex. In many fungal infections mortality is high, particularly if appropriate treatment is delayed (Rautemaa-Richardson and Richardson, 2017). This article introduces common presentations of *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, candidaemia and allergic bronchopulmonary aspergillosis as they may present to the acute medical unit. For each condition, a short scenario is given for the type of presentation the clinician is likely to encounter. The common signs and symptoms, the initial investigations and the initial management are then discussed, to raise awareness of the most common serious fungal diseases.

Pneumocystis jirovecii pneumonia

Clinical scenario

A 32-year-old man with a 6-month history of weight loss, lethargy and recurrent infections was admitted to the acute medical unit with shortness of breath and fever, which he had had for about 3 weeks. The shortness of breath was worse on exertion and he found it difficult to walk even short distances. He was known to have HIV infection but disengaged with care and was not on antiretroviral therapy.

Background

P. jirovecii is a pathogen which colonizes human lungs and causes disease mainly in immunodeficient individuals (Tasaka, 2015). Pneumocystis, previously regarded as a protozoa, is now classified as a fungus (Tasaka, 2015). *P. jirovecii* pneumonia is a common opportunistic infection, seen in patients with HIV-associated immunocompromise and increasingly in other immunocompromised patients, such as those on immunosuppression for autoimmune conditions, transplant recipients, oncology patients or those with chronic lung conditions (Maini et al, 2013). The epidemiology of *P. jirovecii* pneumonia has changed in recent years, with the majority of cases being diagnosed in patients without HIV infection (Patterson et al, 2017). In patients with HIV infection, *P. jirovecii* pneumonia is most likely to occur in patients with a CD4 count of less than 200 cells/mm^3 (Bennett et al, 2015). The majority of the population becomes colonized in childhood (Morris and Norris, 2012). While re-activation of infection is possible, there is evidence to support transmission and disease following re-infection (Nelson et al, 2011; Valade et al, 2015).

Initial investigations

When considering *P. jirovecii* pneumonia as a possible diagnosis, it should be noted that imaging alone is not particularly sensitive or specific for *P. jirovecii* pneumonia. Other infections may mimic the typical radiological appearances of *P. jirovecii* pneumonia (Nelson et al, 2011), including viral and bacterial pneumonia, mycobacterial disease, other fungi and pulmonary Kaposi's sarcoma. On a chest X-ray, the classic appearance of *P. jirovecii* pneumonia is bilateral or diffuse ground-glass opacification (Tasaka, 2015) although occasionally the chest X-ray can be normal, particularly in early disease. Pneumothorax is a recognized complication and is associated with a poor outcome (Pastores et al, 1996; Terzi et al, 2014; Tasaka, 2015). High resolution computed tomography most commonly shows diffuse ground-glass appearances with patchy distribution (Tasaka, 2015). Since the clinical and radiological features of *P. jirovecii* pneumonia are not sufficiently specific, it is important to perform further microbiological investigations to confirm *P. jirovecii* pneumonia and exclude alternative diagnoses or co-pathology (Nelson et al, 2011).

A meta-analysis suggests that measurement of serum levels of 1,3-β-D-glucan, a component of the cell wall of the majority of fungi, including *P. jirovecii*, has a sensitivity of 96% and may have a role as a 'rule-out'

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test (Onishi et al, 2012). Lactate dehydrogenase levels are commonly elevated in patients with *P. jirovecii* pneumonia although this is non-specific (Bennett et al, 2015). Lower respiratory tract samples (bronchoalveolar lavage fluid or induced sputum) should be obtained where possible for microbiological testing.

P. jirovecii cannot be cultured in vitro and methods for visualizing the organism include using either histochemical (typically with Grocott–Gomori methenamine silver stain) or immunofluorescent stains (Nelson et al, 2011), although in practice polymerase chain reaction is increasingly being used for diagnosis in place of these techniques. Bronchoalveolar lavage provides the highest diagnostic yield, with a sensitivity of 98.3% and specificity of 91% from a meta-analysis of Pneumocystis polymerase chain reaction on bronchoalveolar lavage fluid in the diagnosis of *P. jirovecii* pneumonia (Fan et al, 2013). The sensitivity of polymerase chain reaction in induced sputum is variable (Nelson et al, 2011). Lung biopsy (most often by video-assisted thoracoscopic surgery) could be considered for the occasional patient with negative initial tests who is not improving on empirical therapy (diagnostic sensitivity 95–98%), although this is rarely done in practice (Nelson et al, 2011).

Initial management

When *P. jirovecii* pneumonia is suspected, empirical treatment should be started pending investigation results. Factors which indicate a poor clinical outcome in *P. jirovecii* pneumonia include hypoxaemia, concurrent pulmonary infections, elevated lactate dehydrogenase levels, extensive bilateral pulmonary involvement, and an alveolar–arterial gradient of greater than 30 mmHg (Bennett et al, 2015).

Co-trimoxazole (trimethoprim-sulfamethoxazole) remains the first-line treatment for *P. jirovecii* pneumonia, because of its high efficacy and the availability of oral and parenteral forms (Kaplan et al, 2009; Tasaka, 2015). Dosing for treatment of *P. jirovecii* pneumonia should initially be 120 mg/kg daily split into three or four doses, although this can be reduced to 90 mg/kg after 3 days (Nelson et al, 2011). Alternatives to co-trimoxazole include intravenous pentamidine or clindamycin with primaquine, which can be given orally. Glucose 6-phosphate dehydrogenase levels should be checked before using co-trimoxazole or primaquine (Nelson et al, 2011).

Adjunctive corticosteroids should be added in patients with significant hypoxaemia, defined as arterial PaO_2 of 9.3 kPa (70 mmHg) or less (Nelson et al, 2011). Steroids are thought to reduce the likelihood of clinical deterioration resulting from the inflammatory response caused by dying organisms. Duration of therapy (including corticosteroids if used) is 21 days in patients with HIV infection, with most patients starting to respond to treatment within 7 days of therapy. In other patients, such as solid organ transplant recipients or cancer patients, a shorter duration of treatment (14 days) may be effective (Wazir et al, 2004). The evidence for benefit of corticosteroids in *P. jirovecii* pneumonia in patients who are HIV negative is less convincing than in patients with HIV infection, although a meta-analysis was not entirely conclusive (Injean et al, 2017).

Cryptococcal meningitis

Clinical scenario

A 41-year-old woman presented to the acute medical unit with a 3-week history of headache, fever and vomiting. She had a reduced conscious level. She had a past medical history of HIV infection, although adherence to antiretroviral therapy was poor and she disengaged with care. Her last CD4 count 9 months ago was 93 cells/mm^3.

Background

Cryptococcal meningitis is a common opportunistic infection in patients with immunodeficiency (Bicanic and Harrison, 2004). The encapsulated yeast *Cryptococcus neoformans* is an environmental fungus and infection is probably acquired by inhaling small yeast cells (Bicanic and Harrison, 2004). Initial pulmonary infection is often asymptomatic, but the organism may disseminate to extrapulmonary sites, in particular the CNS, depending on host immunity and initial inoculums (Bicanic and Harrison, 2004). Patients are typically immunocompromised, with HIV infection being the most common predisposing factor. Cryptococcosis most commonly presents as subacute meningo-encephalitis, although pneumonia or disseminated disease with numerous umbilicated skin lesions is also well described. In patients with HIV infection, most patients with cryptococcosis have a CD4 count of less than 200 cells/mm^3 (Nelson et al, 2011).

Initial investigations

When cryptococcosis is suspected the most useful screening test is the detection of Cryptococcal antigen, which can be performed on serum (as well as CSF). If the index of suspicion is low, a negative serum Cryptococcal antigen is generally enough to exclude cryptococcosis (Laurenson et al, 1998), although a small number of isolated cases of disseminated disease with negative serum antigen has been reported (Laurenson et al, 1998). Therefore, when cryptococcal meningitis is suspected, lumbar puncture and CSF analysis should be undertaken, irrespective of the serum Cryptococcal antigen. Patients with Cryptococcal meningitis often have an elevated opening pressure, with lymphocytic CSF and an elevated CSF protein. Occasionally, particularly in severely immunocompromised patients, CSF analysis may be normal. Encapsulated yeasts may be seen on microscopy of CSF stained with India ink and *C. neoformans* can be cultured from CSF, blood or occasionally other sites (Bicanic and Harrison, 2004). Poor prognostic features include low CSF white cell count, high titres of Cryptococcal antigen in CSF, raised intracranial pressure and confusion (Saag et al, 1992).

Computed tomography may be normal or show meningeal enhancement, cryptococcomas, oedema or hydrocephalus, but magnetic resonance imaging is more sensitive in detecting cryptococcomas (Bicanic and Harrison, 2004).

Initial management

Early recognition and initiation of treatment is essential to reduce mortality. Treatment for cryptococcal meningitis is intravenous amphotericin B (preferably a liposomal preparation if available) with adjuvant flucytosine (Perfect et al, 2010; Nelson et al, 2011; Loyse et al, 2018; Molloy et al, 2018). The addition of flucytosine increases the speed of sterilization of the CSF and reduces mortality (Perfect et al, 2010; Loyse et al, 2018; Molloy et al, 2018). Generally, at least 2 weeks of induction therapy with intravenous amphotericin B and adjuvant flucytosine is followed by 8 weeks of oral fluconazole as consolidation therapy (Perfect et al, 2010; Nelson et al, 2011).

If progress is slow or there are poor prognostic features, repeat lumbar puncture can be undertaken at 2 weeks, as a positive culture indicates a higher risk of relapse and therefore induction therapy may need to be extended in these cases (Nelson et al, 2011). If CSF opening pressure is greater than 250 mmH_2O, CSF pressure should be reduced by 50% or to 200 mmH_2O. The condition of patients may deteriorate as a result of the consequences of raised intracranial pressure (Graybill et al, 2000). In all patients with cryptococcal meningitis, repeat lumbar puncture should be undertaken if there is neurological deterioration. If the opening pressure is persistently raised, repeated lumbar puncture or a CSF drain or shunt could be considered to reduce the pressure (Bennett et al, 2015). Evidence suggests that starting antiretroviral treatment in patients with cryptococcal meningitis should generally be deferred until after at least 4 weeks of antifungal therapy has been completed to reduce the risk posed by immune reconstitution inflammatory syndrome (Boulware et al, 2014; Eshun-Wilson et al, 2018).

Candidaemia

Clinical scenario

A 32-year-old man was admitted to the acute medical unit with fever and blurry vision, which he had had for 2 weeks. He had a history of Crohn's disease and had previously undergone surgical resection of his small bowel. He was receiving total parenteral nutrition via a Hickmann line, because he had short bowel syndrome.

Background

The incidence of health-care-associated infections caused by *Candida* spp. has risen significantly. *Candida* spp. are normal colonizing flora of the skin, gastrointestinal tract, airways, female genital tract and the urine of patients with indwelling urinary catheters. *Candida* spp. can cause a broad range of infections, from non-life-threatening mucocutaneous infection to invasive infection that can involve almost any organ, often secondary to bloodstream infection. Factors which can predispose patients to developing candidaemia include neutropenia, malignancy, chemotherapy, antimicrobial therapy, parenteral feeding, complicated intra-abdominal surgery, prolonged stay in an intensive care unit and use of intravenous catheters (Kullberg and Arendrup, 2015). Generally, *Candida albicans* tends to be sensitive to fluconazole, while many non-albicans species such as *C. glabrata* and *C. krusei*, which tend to be fluconazole resistant, increase with fluconazole use (Pappas et al, 2003).

Initial investigations

Candida spp. can grow in routine blood cultures, although sensitivity is poor even in patients with confirmed candidaemia. While not in widespread use, there is increasing interest in the use of non-culture-based biomarkers, such as *Candida* polymerase chain reaction or 1,3-β-D-glucan, which provide much greater sensitivity in the diagnosis of invasive candidiasis. A meta-analysis suggests that in patients with probable invasive candidiasis, *Candida* polymerase chain reaction gave a sensitivity of 85% compared with 38% seen with conventional blood cultures (Avni et al, 2011). All patients with confirmed candidaemia should undergo echocardiography to assess for endocarditis and specialist ophthalmology review to assess for chorioretinitis and endophthalmitis (Pappas et al, 2016). In localized disease, biopsy and culture of affected sites could also be considered, such as from the oesophagus via upper gastrointestinal endoscopy.

Initial management

In patients with candidaemia suspected to be secondary to central venous catheter infection, the central venous catheter should be removed as soon as possible. The choice of antifungal treatment depends on the clinical status of the patient, the species identified and previous antifungal exposure. Echinocandins remain the first-line choice in the majority of patients, although alternatives include amphotericin B or triazoles such as fluconazole (Cornely et al, 2012; Pappas et al, 2016). Generally, fluconazole should only be used in patients who are clinically well and have not received therapy with a triazole.

In addition to echocardiography and ophthalmological assessment, surveillance blood cultures should be performed every 48 hours to assess for clearance of candidaemia (Pappas et al, 2016). Treatment duration should be a minimum of 14 days of appropriate antifungal therapy from time of clearance of blood cultures (Cornely et al, 2012; Pappas et al, 2016), assuming that there is no metastatic infection. Assuming the isolate is sensitive, after clearance of blood cultures, oral therapy with fluconazole to complete the course may be appropriate.

Allergic bronchopulmonary aspergillosis

Clinical scenario

A 38-year-old woman with longstanding stable asthma was admitted to the medical admissions unit with pleuritic chest pain and fever. Over the last 2 months she reported worsening wheeze, breathlessness and cough requiring three courses of steroids from her GP with only transient improvement in her symptoms.

KEY POINTS

- Fungal diseases can affect a wide range of patients including immunocompromised patients such as those on immunosuppression for autoimmune conditions, transplant recipients, oncology patients or those with chronic lung diseases.
- First-line treatment for *Pneumocystis jirovecii* pneumonia is high dose co-trimoxazole (trimethoprim-sulfamethoxazole) with adjuvant corticosteroids in patients with significant hypoxaemia.
- Detection of Cryptococcal antigen in serum or CSF is the most useful screening test for cryptococcosis.
- All patients with candidaemia should receive echocardiography, ophthalmological assessment and surveillance blood cultures.
- Allergic bronchopulmonary aspergillosis should be considered in patients with asthma who present with a recent history of unexplained worsening of symptoms.

Background

Allergic bronchopulmonary aspergillosis is caused by a hypersensitivity reaction to inhaled *Aspergillus fumigatus* and affects a small proportion of patients with asthma and cystic fibrosis who are otherwise immunocompetent. Repeated inhalation of *A. fumigatus* leads to colonization (but not invasion) of the chronically inflamed airways of susceptible individuals, and subsequently triggers an inflammatory cascade resulting in the clinical manifestation which includes acute attacks of wheezing, expectoration of brown mucoid plugs or casts, pleuritic chest pain, haemoptysis and fever (Greenberger, 2002; Moss, 2005). Allergic bronchopulmonary aspergillosis should be considered in patients with longstanding stable asthma who present with a recent history of unexplained worsening of symptoms, often having received repeated courses of steroids. Understandably allergic bronchopulmonary aspergillosis can be overlooked and treated as an infective exacerbation in the acute admission setting.

There are five stages of disease (Greenberger, 2002):

- Stage I – acute allergic bronchopulmonary aspergillosis
- Stage II – remission
- Stage III – exacerbation
- Stage IV – corticosteroid-dependent asthma
- Stage V – end-stage lung disease.

Initial investigations

Allergic bronchopulmonary aspergillosis is diagnosed based on the clinical presentation, immunological serological findings and radiological features. In asthmatics, the minimal essential criteria for the diagnosis of allergic bronchopulmonary aspergillosis are:

1. Diagnosis of asthma
2. Presence of central bronchiectasis on high resolution computed tomography
3. Immediate cutaneous reactivity to *A. fumigatus*
4. Elevated total serum IgE levels (greater than 1000 IU/ml)
5. Elevated *A. fumigatus*-specific serum IgE and/or IgG levels (Greenberger, 2002; Moss, 2005; Kosmidis and Denning, 2015).

Additionally, patients will often demonstrate a blood eosinophilia, fleeting pulmonary opacities on chest X-ray particularly in the upper lobes, and on computed tomography bronchial wall thickening, focal air trapping, mucous plugging, atelectasis, and fibrosis or cavitation in advanced stages of disease (Greenberger, 2002). While galactomannan, a polysaccharide component of the *A. fumigatus* cell wall, can be detected in bronchoalveolar lavage fluid, currently there is no evidence to support the role of detection of serum galactomannan in diagnosis of allergic bronchopulmonary aspergillosis (Leonardi et al, 2016).

Initial management

Initial management of these patients should always include thorough assessment and consideration of an acute viral or bacterial cause of their symptoms. If there is clinical suspicion of an acute infection then they should be managed appropriately and treatment based on local hospital policy and antimicrobial guidance. Once a diagnosis of allergic bronchopulmonary aspergillosis is confirmed, the mainstay of treatment is systemic glucocorticoids. Patients require a prolonged course of steroids with a slow wean over several weeks (6–8 weeks) and subsequent regular outpatient assessment on discharge for clinical response to treatment, pulmonary function testing, immunological and radiographical follow up. Patients should be encouraged to consider environmental sources of fungi exposure and provided with recommendations to limit contact. If patients have features of allergic rhinitis, sinusitis or gastro-oesophageal reflux disease, they should be treated appropriately.

Antifungal agents such as itraconazole can be considered as an adjunct in symptomatic individuals who are not responsive to initial steroid therapy, or who become steroid dependent (Moreira et al, 2014). Where itraconazole is not tolerated, voriconazole or posaconazole are alternative options (Patterson et al, 2016). While evidence suggests that antifungal agents can improve disease outcomes, the recommendation is weak (Moreira et al, 2014; Patterson et al, 2016).

Conclusions

Understanding how common fungal diseases can present to an acute medical unit is important for early recognition. Although fungal diseases can be diagnostically challenging, they are relatively common. Understanding the necessary initial investigations and management will improve the prognosis for these patients and reduce the morbidity and mortality associated with a delay in appropriate therapy. **BJHM**

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