CASE REPORT

Dissemination of invasive aspergillosis: diagnostic and management dilemmas

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SUMMARY

Invasive aspergillosis is a highly lethal opportunistic infection that poses a significant threat to immunocompromised patients. With studies suggesting that the incidence of this disease is increasing, and mortality rates remain high, early diagnosis and treatment are very important to improve patient survival. We present a case of a 63-year-old woman on an immunosuppression regimen with methylprednisolone and azathioprine for the treatment of autoimmune hepatitis, who presented with neurological and respiratory symptoms leading to a rapid clinical decline. A final diagnosis of disseminated invasive aspergillosis was made at autopsy. This case emphasises the importance in maintaining a high index of suspicion to ensure that the proper workup, diagnosis and treatment can be initiated earlier in the clinical presentation in an effort to decrease the extremely high mortality in these cases.

BACKGROUND

Aspergillus species are ubiquitous fungus in the external environment and inhalation of infectious conidia is a common event; however, tissue invasion, or invasive aspergillosis, is uncommon. Invasive aspergillosis occurs most frequently in the setting of immunosuppression and is a rapidly progressive, frequently fatal disease. Patients at risk include those with prolonged neutropenia, recipients of haematopoietic stem-cell transplants or solid-organ transplants and patients with advanced AIDS or chronic granulomatous disease. Also at risk, but rarely seen, are patients with serious autoimmune disorders being treated with intensive immunosuppressive regimens.¹ The profile of patients considered immunocompromised continues to expand and despite advances in diagnosis and treatment, invasive aspergillosis remains a devastating opportunistic infection. The overall case-fatality rate (CFR) was systematically reviewed by Lin *et al*² in 2001 and found to be 58%. For patients with central nervous system or disseminated aspergillosis, as in this case, the CFR was 88.1%.

CASE PRESENTATION

A 63-year-old woman with a medical history of hypertension, diabetes mellitus type II, recently diagnosed autoimmune hepatitis, associated with hepatic encephalopathy, on methylprednisolone for approximately 1 month and azathioprine for 1 week presented with generalised weakness, malaise and increased confusion for 5 days. The

patient's family noted slowing of her speech with occasional dysarthria, and were concerned because she had a recent unwitnessed fall and became relatively sedentary. The patient also reported of a productive cough for a few days without fevers or chills. Vitals were remarkable for respiratory rate of 20 respirations per min, oxygen saturation of 92% on room air, heart rate of 119 bpm, and blood pressure of 100/50 mm Hg. On physical examination the patient did not appear in distress. On lung examination there were bilateral diffuse rales. A holosystolic murmur, grade 3/6, was heard at the left lower sternal border. The neurological examination was normal except for mild bradykinesia.

INVESTIGATIONS

Laboratory findings were significant for leucocytosis (white cell count 22.03 K/ μ L), anaemia (haemoglobin 10.8 g/dL), thrombocytopenia (platelets 63 K/ μ L), elevated liver function tests (alkaline phosphatase 184 U/L, aspartate aminotransferase 58 U/L, alanine transaminase 61 U/L), elevated bilirubin (3.8 mg/dL), elevated ammonia (114 μ mol/L), and elevated lactic acid (9 mm/L). A chest radiograph revealed extensive bilateral pulmonary opacities (figure 1). CT lung showed multifocal pulmonary opacities in all lobes, consolidation and/or masses, some with cavitation (figure 2). CT head showed several hypodense parenchymal lesions, new compared with prior examination; largest in the left temporal lobe (1.4 cm), right frontal lobe (1.2 cm), junction of right occipital and temporal lobes (1.1 cm), and inferiorly in the right frontal lobe (5 mm) (figure 3). A transthoracic echocardiogram showed no definite evidence of vegetation. A bronchoscopy with bronchial alveolar lavage (BAL) demonstrated few secretions and the bronchial washing specimen revealed marked acute inflammation that was negative for malignant cells. BAL specimen testing was negative for viral antigens, *Legionella*, *Pneumocystis jiroveci* and acid-fast bacilli. The culture grew 3000 cfu/mL *Candida albicans* and approximately 5000 cfu/mL *Streptococcus viridans*. Influenza nasopharyngeal swab test was negative. Final blood cultures and sputum cultures were also negative.

DIFFERENTIAL DIAGNOSIS

- Healthcare associated pneumonia
- Endocarditis with septic emboli phenomenon
- See further discussion in treatment section

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Figure 1 Chest X-ray.

TREATMENT

The patient was admitted to the intensive care unit (ICU) for severe sepsis secondary to healthcare associated pneumonia versus endocarditis with septic emboli phenomenon and started on broad-spectrum antibiotics (vancomycin and cefepime). On hospital day 2, the patient became somnolent with increasing FiO_2 requirements and was intubated for declining mental status and hypoxic respiratory failure. At this point a definitive diagnosis was not performed. Cultures were negative and despite maximum ICU care, the patient's condition rapidly declined. Antibiotic coverage was broadened to meropenem and vancomycin for the possibility of a resistant bacterial infection, and empiric micafungin was added for antifungal coverage. A video-assisted thoracoscopic surgery lung biopsy was considered, however, the patient was too unstable for the procedure.

OUTCOME AND FOLLOW-UP

On hospital day 3 the patient clinically worsened with development of septic shock, requiring maximum pressor support with norepinephrine, vasopressin and phenylephrine. Shortly thereafter, the patient expired. Autopsy revealed multiple necrotic, cavitary and consolidated lung lesions up to $5 \times 4 \times 3$ cm, involving all lobes, with fungal hyphae penetrating the pleura seen on H&E stain (figure 4). Multiple bilateral foci of invasive hyphae were visible on Gomori methenamine silver (GMS) stain in the brain involving the occipital, temporal, parietal and frontal cortices (figure 5). Invasive fungal hyphae were also found in the thyroid, heart and right kidney. A postmortem fungal culture from the lung grew *Aspergillus fumigatus*, consistent with the

Figure 2 Chest CT.

Figure 3 Head CT.

morphology seen in the organs. The patient's clinical presentation of rapid deterioration of mental status and respiratory failure was consistent with the diagnosis of disseminated aspergillosis.

DISCUSSION

In this case, immunosuppression for autoimmune hepatitis most likely contributed to the tissue invasion of aspergillosis. As illustrated in our case, invasive aspergillosis is challenging to diagnose. The presentation is based on sites of infection, with the lung being the most common organ. Other less common sites include the sinuses, gastrointestinal (GI) tract or skin. Invasive pulmonary aspergillosis presents with non-specific symptoms usually mimicking bronchopneumonia. As seen in our patient the infection may also disseminate haematogenously to other organs. It most often disseminates to the brain, but also to the skin, thyroid, bone, kidneys, liver, GI tract, eye and heart. Histopathological examination with microbiological confirmation remains the gold standard in diagnosis; however, it is often difficult or not feasible to obtain a biopsy specimen. The histological findings characteristic of aspergillosis are septated hyaline hyphae with acute angle (45°) dichotomous branching visible with H&E or GMS staining.³ Blood cultures are rarely positive and sputum cultures are of limited value. *Aspergillus* species may be found in the sputum in up to 15% of healthy people, however, up to 70% of those confirmed with invasive

Figure 4 Lung H&E stain.

Figure 5 Brain Gomori methenamine silver (GMS) stain.

aspergillosis have a negative sputum result. The isolation of *Aspergillus* species from BAL fluid from immunosuppressed patients is highly indicative of invasive aspergillosis (97% specificity), but is only positive in 50–58% of patients. In addition to the lack of sensitivity, the diagnosis may be delayed since it may take a few days to grow from culture.⁴ Therefore it is not unusual to have negative results, as in our case, making it essential to keep a high index of suspicion and to empirically treat, especially in the setting of an immunocompromised host. Owing to limitations of the conventional diagnostic techniques, other modalities for diagnosis have been developed and are an area of current research. The two commercially available assays are galactomannan (GM) or β -(1,3)-D-glucan (BDG), both of which are components of the fungal cell wall. The GM assay is relatively specific for invasive aspergillosis. In a meta-analysis, the GM assay had a sensitivity of 71% and a specificity of 89%. The BDG assay also detects other invasive fungal diseases, with the most complete study showing a sensitivity of 64% and specificity of 84%. Currently these tests can be used in combination with several diagnostic techniques to rule out a fungal infection in patients at risk. Techniques using fungal nucleic acid detection, mostly based on PCR still remain investigational.⁵ Early initiation of antifungal therapy in patients with highly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted. Based on the largest randomised controlled trial, it is recommended that voriconazole be used for the primary treatment for invasive aspergillosis. It has also been used in enough cases of extrapulmonary and disseminated infection to infer it is effective in these cases as well. Alternatives to voriconazole are the formulations of amphotericin B, itraconazole and caspofungin. Micafungin, which was started empirically in our patient, is also a member of the class of echinocandins. It has in vitro, in vivo, and clinical activity against aspergillosis, but is not

licensed in the USA for this indication.⁶ Despite improvements in diagnosis and the advent of voriconazole and newer formulations of amphotericin B, mortality from invasive aspergillosis remains high. Underlying patient conditions and the site of infection remain important prognostic factors. In our case, given the rapid clinical decline and the extent of disease seen on autopsy, it is unlikely that voriconazole or one of the salvage treatments would have changed the outcome. Clinicians should be aware of this case and others like it when prescribing immunosuppressive therapy. With the increase of immunocompromised patients we continue to strive for better diagnostic and treatment options. We need to consider opportunistic fungal infections such as aspergillosis as a possible diagnosis and initiate early treatment to improve patient survival in these cases.

Learning points

- ▶ Owing to the increase in the incidence of haematopoietic stem-cell transplants, solid-organ transplants and the expanding profile of immunocompromised patients, invasive and disseminated aspergillosis has become more prevalent and physicians will manage these patients more and more frequently in the future.
- ▶ Since diagnosis can be challenging and timely, empiric treatment in patients with strongly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted.
- ▶ This case emphasises the importance in maintaining a high index of suspicion to ensure that the proper workup, diagnosis and treatment can be initiated earlier in the clinical presentation in an effort to decrease the extremely high mortality of these cases.

Competing interests None.

Patient consent Obtained.

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