CASE REPORT

An unusual case of invasive aspergillosis in an immunocompetent individual

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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 the case of a 33-year-old immunocompetent woman who presented with a history of cough and severe breathlessness, and was diagnosed to have invasive aspergillosis. This case emphasises the importance of maintaining a high index of suspicion and also of remembering that invasive aspergillosis is no longer only a disease of immunocompromised individuals. In addition, this case tells us that aspergillosis is one of the new emerging infections in intensive care units.

BACKGROUND

Aspergillus spp are ubiquitous fungi 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 neutropaenia, recipients of haematopoietic stem cell transplants or solid-organ transplants and those 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.

Despite the usual presentation, aspergillosis may also, in rare situations, occur in immunocompetent individuals, which compelled us to highlight this case.

CASE PRESENTATION

A 33-year-old housewife with no premorbidities presented with sudden onset of breathlessness after a 4-day history of cough and fever. On examination, she was febrile and tachypnoeic, with oxygen saturation of 84% on high-flow oxygen. Respiratory system examination showed bronchial breath sounds in left supraclavicular and interscapular areas; all other systems were within normal limits. Hence a clinical diagnosis of left upper lobe pneumonia with acute respiratory distress syndrome (ARDS) was initially made, based on the presentation.

INVESTIGATIONS

Laboratory investigations showed normal white cell counts (WCC) with mildly elevated erythrocyte

sedimentation rate (31 mm/h) and mild elevation of aspartate aminotransferase/alanine transaminase (144/152 U/L) levels. Other routine blood parameters were normal. Initial workup for fever, including malaria, dengue, scrub typhus and leptospirosis tests, were negative, thereby ruling out the other common causes of ARDS prevalent in the locality. Hepatitis B surface antigen and HIV were also negative. Chest X-ray showed left hemithorax haziness (figure 1). ECG showed sinus tachycardia and two-dimensional echocardiography was normal. Ultrasound study of the abdomen was normal. Arterial blood gases showed respiratory alkalosis with PO₂/FiO₂ of 121. A clinical diagnosis of left upper lobe pneumonia with ARDS was considered, and the patient was started on broad-spectrum antibiotics. She was also started on oseltamivir, after collecting respiratory samples, in view of the possibility of H1N1 influenza, which is commonly seen at that time of the year in our community.

As the patient continued to be tachypnoeic and subsequent investigations showed increasing WCC, she was electively intubated and antibiotics were escalated. Meanwhile, blood and urine cultures were reported as sterile, and viral studies were negative for influenza and other common respiratory viruses. Sputum samples for acid-fast bacilli were reported as negative. On the fourth day of

Figure 1 Left hemithorax homogeneous opacity.

CrossMark

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Figure 2 Focal and patchy areas of consolidation (with areas of breakdown), ground glass attenuation and a few random nodules diffusely scattered in both lungs, the largest area being in left upper lobe. Bilateral mild pleural effusion.

admission, the patient's sputum culture was reported as positive for *Aspergillus fumigatus*. Since we considered that as possibly a normal upper respiratory commensal, a repeat culture of endotracheal aspirate was sent. When that was also reported as positive for the same organism the next day, the patient was started on intravenous voriconazole with intravenous caspofungin, after sending for a repeat blood culture and *Aspergillus* galactomannan antigen assay.

CT scan of the thorax was suggestive of an acute infective aetiology in both lungs, predominantly in the left upper lobe (figure 2). A CT scan of the osteomeatal complex was carried out to look for the source of infection from paranasal sinuses, and was normal (figure 3). PCR for *Pneumocystis jirovecii*, antinuclear antibody profile, immunoglobulin and complement levels, were within normal limits, ruling out any immunocompromised status. A transbronchial lung biopsy could not be performed as we do not have that facility in our setting.

After starting voriconazole and caspofungin, the patient started showing improvement clinically; investigation reports also showed signs of recovery. *Aspergillus* galactomannan antigen ELISA was reported as positive, confirming evidence of

Figure 3 Normal CT of the osteomeatal complex.

invasive aspergillosis. The patient was extubated after 7 days of intravenous antifungal therapy and repeat sputum culture was sterile. She was discharged from the hospital uneventfully and followed up after 2 weeks, with blood counts and chest X-ray, which were completely normal.

DIFFERENTIAL DIAGNOSIS

- Community acquired pneumonia
- ARDS

TREATMENT

The standard regimen for initial therapy of invasive aspergillosis diagnosed by culture, galactomannan antigen or histopathology, is a combination therapy with azole and an echinocandin. In our patient, we choose to give the above regimen using voriconazole and caspofungin; the patient responded well to the treatment, with no complications.

OUTCOME AND FOLLOW-UP

The patient recovered completely after the appropriate regimen for aspergillosis and on follow-up after 2 weeks of discharge she was asymptomatic and her chest X-ray was completely normal.

DISCUSSION

As illustrated in our case, invasive aspergillosis is challenging to diagnose. The presentation is based on sites of infection, with lungs 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.¹ It is also important to note that the classical 'halo' sign seen on CT scan of the thorax is common in immunocompromised hosts, but often not noticed in immunocompetent hosts.² This makes the diagnosis even more challenging in immunocompetent hosts.

Invasive pulmonary aspergillosis most often disseminates to the brain, however, it may also spread to the skin, thyroid, bone, kidneys, liver, GI tract, eyes or 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, as in our case. The histological findings characteristic of aspergillosis are septated hyaline hyphae with acute angle (45°) dichotomous branching visible with H&E or Grocott's methenamine silver staining.³

Blood cultures are rarely positive and sputum cultures are of limited value. *Aspergillus* spp may be found in the sputum in up to 15% of healthy people, however, up to 70% of those confirmed with invasive aspergillosis have a negative sputum result. The isolation of *Aspergillus* spp from bronchoalveolar lavage fluid from immunosuppressed patients is highly indicative of invasive aspergillosis (97% specificity), but is only positive in 50–58% of patients.⁴ In addition to the lack of sensitivity, the diagnosis may be delayed, since it may take a few days to grow from culture. Therefore, it is usual to receive negative results, especially in the setting of an immunocompetent host, but a high index of suspicion made us workup this case for detection of aspergillosis.

Owing to the 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 and β -(1,3)-d-glucan (BDG), both of which are components of the fungal cell wall. The galactomannan assay is relatively specific for invasive aspergillosis. In a meta-analysis, the galactomannan 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%.⁵ 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.

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 voriconazole⁶ be used for the primary treatment of invasive aspergillosis. It has also been used in many cases of extrapulmonary and disseminated infection, inferring it is effective in these cases as well. Alternatives to voriconazole are the formulations of amphotericin B, itraconazole and caspofungin.

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Competing interests None declared.

Patient consent Obtained.

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Patient's perspective

- ▶ Lung infection with invasive aspergillosis is a rare condition in those without diabetes, cancer and other such serious conditions.
- ▶ I was lucky to be diagnosed with this disease at the right time so that correct treatment could be started for my recovery. Those initial few days in the ICU immediately before and during mechanical ventilation were very scary.

Learning points

- ▶ Invasive aspergillosis has always been considered as an infection expressly of immunocompromised individuals.
- ▶ It is an emerging infection in the intensive care units and must be in our spectrum of differential diagnosis in immunocompetent individuals as well, especially when the patient does not respond to initial treatment.
- ▶ The classical 'halo' sign of invasive aspergillosis on CT scan of the thorax is often absent in immunocompetent hosts and diagnosis requires a very high degree of suspicion.
- ▶ Voriconazole in combination with an echinocandin shows good response in invasive aspergillosis.

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