Favourable outcome of combined medical surgical treatment of cerebral aspergillosis of pulmonary origin

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Introduction: Cerebral aspergillosis is a highly fatal infection. Its origin is most likely blood-borne from the lungs and most patients are immunosuppressed. Mortality is over 90 % and the treatment chosen is key for survival.

Case presentation: We report a 32-year-old female with a history of acute myeloid leukaemia (M3) who was admitted to the hospital due to a nodular infiltrate in the right superior lobe. A lung computed tomography (CT) scan displayed a right upper lobe cavitated nodule. A brain CT scan showed a right hemisphere deep abscess. Pulmonary aspergillosis was diagnosed after bronchoalveolar lavage. Three weeks later, while on antifungal treatment with voriconazole and liposomal amphotericin B, she suffered left motor focal deficits, and brain abscess puncture and aspiration by neuronavigation were performed for diagnosis and decompression. A PCR assay was positive for Aspergillus fumigatus. One week later, she developed an intraventricular brain haemorrhage requiring external ventricular drainage and intrathecal fibrinolysis with recombinant tissue plasminogen activator. She eventually achieved a good neurological outcome. A control brain CT showed an important reduction in mass size.

Conclusion: Antifungal treatment is the mainstay for brain abscess treatment, and its combination with stereotactic needle aspiration is a better option compared with open surgery, particularly in abscesses located in deep motor areas.

Keywords: Aspergillus fumigatus; Cerebral aspergillosis.

Introduction

Central nervous system aspergillosis is a highly fatal infection and the lung is usually its primary focus (Brouwer et al., 2014; Kourkoumpetis et al., 2012; Marr et al., 2015; Spapen et al., 2014). Pathogenic mechanisms of infection are dependent on predisposing conditions. Haematopoietic cancer is often associated with tuberculosis or non-bacterial causes of infection, such as fungi or parasites (Brouwer et al., 2014). Patient mortality is high in the literature, being over 90 % in most of the published case series, and one of the most important modifiable mortality factors is the treatment chosen: medical versus combined medical and surgical. The best clinical approach is still a matter of debate. We present the case of a young woman with leukaemia and cerebral aspergillosis secondary to a primary lung infection with an excellent outcome, who received a combined medical and surgical treatment.

Case report

The patient was a 32-year-old female with a history of acute myeloid leukaemia (M3) diagnosed in September 2013 and treated with all-trans retinoic acid. She was discharged on 15 October 2013 but readmitted to the hospital 1 week later due to fever and dyspnoea. A chest X-ray showed a nodular infiltrate in the right superior lobe. Treatment with cefepime and teicoplanin was started but,
because of persistent fever, was quickly changed to meropenem and linezolid. Four days after admission, neurological symptoms arose: sleepiness and vomiting without focal deficits. A brain computed tomography (CT) scan (Fig. 1) was performed and a deep abscess in right hemisphere was found. A lung CT (Fig. 2) was also performed and showed a right upper lobe cavitated nodule radiologically suggestive of fungal pulmonary infection. The patient was then transferred to the intensive care unit (ICU).

A bronchoscopic study was performed, and a very positive index value of 10.07 for galactomannan antigen levels was detected in a bronchoalveolar lavage. An antimicrobial spectrum increase was decided, and a combination of antifungal treatment (Marr et al., 2015) with intravenous voriconazole (4 mg kg\(^{-1}\) 400 mg every 12 h after a loading dose of 6 mg kg\(^{-1}\) every 12 h) and liposomal amphotericin B (5 mg kg\(^{-1}\) daily intravenously) were added preemptively to the treatment.

Three weeks after ICU admission and while on antifungal treatment, the patient suddenly suffered left motor focal deficits, and brain abscess puncture and aspiration by neuronavigation were performed for diagnosis and decompression (Brouwer et al., 2014). There were no complications after brain abscess drainage. A Gram stain of the brain collection revealed septate hyphae; however, the mycological culture was negative. The sample was sent to the Spanish National Centre for Microbiology (Instituto de Salud Carlos III, Madrid, Spain), where a multiplex PCR assay designed to detect \textit{Aspergillus fumigatus}, \textit{Aspergillus flavus} and \textit{Aspergillus terreus} DNA was performed, as described previously (Buitrago et al., 2014). The assay was positive for \textit{A. fumigatus}.

The patient was also diagnosed with internal iliac vein thrombosis, and a low-molecular-mass heparin treatment was started a few days after surgery. In week 4 after ICU admission, the patient had impairment of consciousness and eventually entered a deep coma requiring endotracheal intubation and mechanical ventilation. A brain CT was performed and an intraventricular brain haemorrhage was found, requiring an external ventricular drain (Fig. 3), and intrathecal fibrinolysis treatment with recombinant tissue plasminogen activator was started with an initial dose of 2 mg followed 8 h later by three 1 mg additional doses every 12 h, with a good radiological and clinical response. No intrathecal antifungals were given.

In week 6 after ICU admission, the patient was extubated and 2 weeks later she was discharged to the general ward and eventually discharged from the hospital 4 months later after a protracted clinical course following her leukaemia consolidation treatment. The patient recovered and achieved a good neurological outcome, being independent for daily activity. A control brain CT showed radiological improvement and an important reduction in mass size with peripheral cavitation after intravenous contrast administration. Antifungal treatment with voriconazole was given for 4 months, which was changed to the oral route 68 days after starting intravenous treatment. Liposomal amphotericin B had been previously discontinued, 49 days after starting its treatment.

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**Fig. 1.** Axial CT image of the cranium showing a deep right hemispheric abscess (arrow) characterized by a hypodense centre and an isodense ring, after intravenous contrast administration.

**Fig. 2.** Lung CT scan displaying a right upper lobe cavitated nodule (arrow).
Discussion

In most patients, brain abscesses result from predisposing factors or from underlying diseases, such as in this case with a history of acute leukemia. Micro-organisms enter in the brain through contiguous spread in about half of cases and through haematogenous dissemination in about one-third of cases. In our case, blood spread came from a pulmonary aspergillosis.

There are few or no data from prospective controlled clinical studies available to support the use of higher doses of single antifungal agents, combination of agents, intrathecal or intralesional antifungal chemotherapy, or the use of immunomodulators in brain abscess cases. Combination of voriconazole and other antifungals has recently been shown to be useful in invasive aspergillosis. The treatment of invasive aspergillosis with a combination of voriconazole and anidulafungin was shown to be associated with a non-significant but clinically meaningful survival benefit in patients with haematological malignancies or haematopoietic cell transplantation (Marr et al., 2015).

Voriconazole has also been used either alone or in combination with other antifungals in cerebral aspergillosis, but very few patients received the drug as first-line treatment (Spapen et al., 2014). In our case, the patient’s serious clinical condition, with pulmonary and central nervous system invasive aspergillosis, in addition to the scarce or null therapeutic responses in similar situations published in the literature, prompted us to choose a salvage therapy with two antifungals, each with a target effect on the two affected organs: liposomal amphotericin B for the lungs and voriconazole for the brain.

Neurosurgery is used for the identification of the causative pathogen and for reducing the size of the abscess (Brouwer et al., 2014). No clinical improvement, new neurological symptoms or a progressive increase in the abscess ring diameter are indications for surgical treatment. Stereotactic navigation and abscess drainage are preferable to surgical excision, particularly in ‘eloquent’ brain tissue (speech, movement, sensation and vision areas) (Brouwer et al., 2014).

Invasive cerebral aspergillosis is the most lethal manifestation of invasive *Aspergillus* infection and has historically been associated with a mortality rate close to 90%, regardless of the immune status of the patient. This serious prognosis highlights the outstanding outcome of a combined medical and surgical treatment approach in our patient.

*Aspergillus* infection of the brain almost always represents a coincidental finding in critically ill patients. Its origin is most likely blood-borne from the lungs, and most patients usually are immunosuppressed, as was the situation in our case. The clinical presentation is usually subtle and, apart from unexplained fever, mostly devoid of ‘classical’ neurological manifestations. For diagnosis of intracerebral abscess, physicians ought to couple a high index of suspicion in immunocompromised patients with a combination of serological, microbiological and radiological tests. The weight of evidence supports voriconazole as first-line treatment for intracerebral abscess.

The current case focuses attention on the use of combined voriconazole and liposomal amphotericin B with minimally invasive neurosurgical treatment, which improved the patient’s outcome, in spite of serious clinical complications. Antifungal treatment is the mainstay for brain abscess treatment, and its combination with stereotactic needle aspiration seems to be a better option compared with open surgery, particularly in abscesses located deep in the brain, or near to speech or motor areas. These patients also need an extended period of antifungal treatment.

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References


