CASE REPORT

Aspergillus niger infection in an immunosuppressed patient confined solely to the brainLucy Simmonds,¹ Sian Mitchell,¹ Barrie White,¹ Shanika A Cruz,² David Denning³¹Department of Neurosurgery, Queen's Medical Centre, Nottingham, UK²Department of Microbiology, Queen's Medical Centre, Nottingham, UK³University Hospital of South Manchester, UK**Correspondence to**Dr Lucy Simmonds,
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SUMMARY

A 68-year-old woman with a background of hypertension, stroke and rheumatoid arthritis presented to her local hospital after a 4-week history of gradual deterioration and increasing confusion with new onset right-sided weakness. Her initial CT scan revealed a rim enhancing mass lesion with surrounding oedema in the left parietal lobe for which she underwent CT stealth-guided biopsy. Microbiology culture of the 2 biopsy samples yielded *Aspergillus niger* and she was started on the antifungal agent voriconazole. MRI 2 weeks after the procedure also demonstrated radiological findings consistent with intracranial aspergillosis. She later developed leucopenia with neutrophils of $1.5 \times 10^9/L$ and her methotrexate and voriconazole were stopped. Voriconazole was changed to oral posaconazole. She did not undergo surgical resection and has continued to improve clinically on posaconazole, with recovery in her white cell count.

BACKGROUND

Cerebral aspergillosis is an uncommon infection associated with high morbidity and mortality and there are few presented cases with good outcome. This case highlights non-surgical treatment of cerebral aspergillosis in a patient with rheumatoid arthritis in a tertiary neurosurgical unit. Furthermore, invasive infection with this particular species is thought to be highly unusual given the fact that its larger conidia do not readily reach deep into lung tissues. Therefore, although our patient was taking immunosuppressive medication, it is notable that there was no lung or sinus involvement in this case. This case has been presented to share the non-surgical approach used in this patient with cerebral aspergillosis with a good clinical outcome.

CASE PRESENTATION

A 68-year-old retired woman was transferred to a tertiary neurosurgical unit from her local hospital after presenting with a 4-week history of gradual deterioration, expressive and receptive dysphasia, increasing confusion and new onset right-sided weakness. She had a longstanding history of hypertension, previous stroke and rheumatoid arthritis for which she was taking hydroxychloroquine, sulfasalazine and methotrexate once weekly. Prior to her hospital admission, she lived alone and has no significant family history.

INVESTIGATIONS

Regular brain imaging has been pivotal in this patient's case. On admission to her local hospital,

her CT scan and subsequent MRI revealed a deep left parietal mass lesion, with significant surrounding vasogenic oedema and associated mild left lateral ventricle compression (figure 1). She was transferred to the neurosurgical unit after discussion at the multidisciplinary team meeting (MDT) for biopsy of the parietal lesion 9 days after presentation. Initially, the differential diagnosis was necrotic tumour (glioblastoma multiforme) or pyogenic abscess. However, the biopsy did not yield any pus or viable tumour. MRI was repeated 2 days after the biopsy which confirmed that the biopsy sample had been taken from the centre of the lesion.

The growth of *Aspergillus niger* on direct microbiology culture plates was unexpected. While the panfungal PCR testing was negative (a negative result does not preclude the diagnosis of invasive aspergillosis), the direct fungal growth on all streaks of the inoculum from two separate biopsy samples was deemed significant.

The patient had already been treated with 4 mg oral dexamethasone four times a day for 14 days postbiopsy which correlated with a clinical improvement and lessening of the oedema, but minor extension of the lesion was seen on MRI at 11 days postbiopsy. Five days later, a further MRI

Figure 1 CT head without contrast, taken at the time of presentation. Both CT and MRI demonstrated a round intra-axial lesion with vasogenic oedema in the left parietal lobe, with associated mild left lateral ventricle compression and 5.5 mm midline shift to the right.

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showed multifocal haemorrhagic leucoencephalitis which was reported as consistent with aspergillosis. At 23 days after the biopsy, the patient's right-sided weakness became suddenly more severe but an urgent CT head without contrast showed no new haemorrhage or ischaemia and the midline shift had mostly resolved. The weakness steadily improved with physiotherapy. Two further inpatient MRIs at 1 month and 6 weeks postbiopsy showed no progression of the disease.

CT of the chest, abdomen and pelvis showed no foci of infection (specifically in the lungs or the gastrointestinal tract) or primary malignancy. She had no symptoms or radiological signs of sinus infection and there was no evidence of skin infection on examination.

Serum 1,3- β -glucan was negative and it was not safe to perform a lumbar puncture to obtain cerebrospinal fluid for galactomannan testing.

Therapeutic antifungal drug-level monitoring was used to ensure adequate serum levels, in line with guidance on prolonged use of triazole antifungals.¹

DIFFERENTIAL DIAGNOSIS

The prevailing decision of the neuro-oncology MDT was that the mass seen on CT was highly likely to be a high-grade glioma, but lymphoma and metastases were also suggested. As the lesion was deep seated, it would have been too dangerous and of little benefit to resect had it been a high-grade glioma. Central nervous system (CNS) *Aspergillus* can vary in its presentation on imaging, but can include, oedema, haemorrhagic lesions, solid lesions (aspergillomas) and appearances of infarction.² Frozen histological sections sent from the biopsy in this case were difficult to interpret and could not differentiate between tumour and an abscess. Fungal histological stains were negative (but are known to have a low sensitivity).

Fungal culture is advised for all suspicious lesions as the incidence of fungal brain abscess has increased due to the increased use of immunosuppressant drugs (including high-dose corticosteroids) and broad-spectrum antibacterials. While *Candida* species are the most common causative agents in postmortem studies, in addition to *Aspergillus* species, cerebral mucormycosis (zygomycosis) and infection with other fungal species can occur and as in this case, the diagnosis is often unexpected.³

TREATMENT

Following microbiological confirmation of the organism, the patient was loaded with two doses of voriconazole 400 mg, in tablet form. She was then continued on 200 mg twice daily; however, this coincided with a sudden drop in the neutrophil count. Leucopenia is a known side effect of this medication, so it was stopped after 10 days, and her methotrexate temporarily withheld. She was started on oral posaconazole tablets 300 mg (twice daily for the first 24 hours, and then once daily), another triazole antifungal indicated for invasive *Aspergillus* infection. This was associated with a gradual return of her white cell count to normal levels and continued clinical improvement.

This case was discussed with Professor David Denning at the National Aspergillosis Centre, who provided clinical guidance throughout and is following up the patient in his outpatient clinic given the complexity and challenges of such cases and the need for prolonged antifungal therapy.

OUTCOME AND FOLLOW-UP

Subjectively her confusion and dysphasia has improved, although she remained below her premorbid baseline when she

was repatriated to her local hospital for rehabilitation. She is likely to remain on treatment for several months and continue to have monitoring MRIs. There is no current indication for surgical intervention. This report is written 8 months after presentation.

DISCUSSION

Central nervous system aspergillosis has a poor prognosis with the variable mortality rate quoted in the literature being as high as 86%.⁴ Most patients who develop intracerebral aspergillosis are immunosuppressed, and in these patients, the primary source of the infection is most commonly the lungs⁴ following inhalation as the route of entry. *A. niger* is an environmental organism found in soil, on plants and even in some food and condiments such as pepper. Haematogenous spread to the brain is associated with poorer outcome than direct spread from sinusitis or craniofacial trauma.⁴ Mortality from cerebral aspergillosis in non-immunosuppressed patients is considerably lower—13%.⁵

A case similar to ours has been described⁶ of a patient also taking immunosuppressants for rheumatoid arthritis, who developed pulmonary and cerebral *Aspergillus* infection and was treated with oral voriconazole but required the addition of intravenous amphotericin B. At follow-up, 10 months after diagnosis, the patient was clinically well and the brain lesions had resolved. The Infectious Diseases Society of America (ISDA)¹ recommend voriconazole as first-line treatment of CNS aspergillosis and liposomal amphotericin B (which penetrates less well) only if voriconazole cannot be tolerated or the disease is refractory to voriconazole. Isavuconazole is a new extended spectrum triazole antifungal drug which is also recommended as an alternative treatment of invasive aspergillosis;¹ however, *A. niger* appears to be less susceptible than other *Aspergillus* species.⁷ Isavuconazole is as effective as amphotericin B in treating invasive mucormycosis⁸ and either could be considered for empirical therapy while awaiting the microbiology results.

Therapeutic drug monitoring is particularly important as many affected patients may be taking immunosuppressant drugs which have the potential to interact with triazoles.¹

One of the largest studies of CNS aspergillosis, involving 81 patients who received voriconazole treatment, showed that 31% of patients were still alive at follow-up at just over 1 year.⁹ There are case reports suggesting that newer antifungal drugs such as voriconazole can contribute to improved outcomes;⁹ however, lesions may take many months (up to 30 in one case) to resolve radiologically.⁴

Learning points

- Mass lesions of the brain are not always tumours and comprehensive microbiology and histopathology investigations are required.
- Mortality is high among patients with intracerebral aspergillosis, and more so in the immunosuppressed, but there are reports of successful treatment with antifungal drugs.
- Cerebral *Aspergillus* infection may occur in the absence of primary infection in the sinuses or chest.
- MRI is the imaging modality of choice and should be repeated at regular intervals to assess the response to treatment, which may take many months.

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REFERENCES

- 1 Patterson TF, Thompson GR, Denning DW, *et al.* Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016;63:e1–60. <http://cid.oxfordjournals.org/content/early/2016/06/22/cid.ciw326.full.pdf+html> (accessed 17/01/17).
- 2 Kastrup O, Wanke I, Maschke M. Neuroimaging of infections. *NeuroRx* 2005;2:324–32.
- 3 Mandell GL, Bennett JE, Dolin R. *Principles and practice of infectious diseases*. 7th edn. Philadelphia: Elsevier, 2010.
- 4 Marzolf G, Sabou M, Lannes B, *et al.* Magnetic resonance imaging of cerebral aspergillosis: imaging and pathological correlations. *PLoS ONE* 2016;11:e0152475.
- 5 Denning D. Therapeutic outcomes in invasive aspergillosis. *Clin Infect Dis* 1996;23:608–1.
- 6 Ehrmann S, Bastides F, Gissot V, *et al.* Cerebral aspergillosis in the critically ill: two cases of successful medical treatment. *Intensive Care Med* 2005;31:738–42.
- 7 Howard SJ, Lass-Flörl C, Cuenca-Estrella M, *et al.* Determination of isavuconazole susceptibility of *Aspergillus* and *Candida* species by the EUCAST method. *Antimicrob Agents Chemother* 2013;57:5426–31.
- 8 Vehreschild MJGT, Vehreschild JJ, Marty FM, *et al.* Primary treatment of invasive mucormycosis (IM) with isavuconazole (VITAL Study) or amphotericin formulations (FungiScope): case matched analysis. *Blood* 2014;124:1151.
- 9 Schwartz S, Ruhnke M, Ribaud B, *et al.* Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood* 2005;106:2641–5.

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