

Aspergillus flavus-Induced Brain Abscess in an Immunocompetent Child

Case report

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ارشاشيات فلافس المستحثة للخراج في دماغ طفل ذو كفاءة مناعية تقرير الحالة

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ABSTRACT: Intracranial aspergillosis is an extremely rare manifestation of invasive aspergillosis in immunocompetent children and is associated with high morbidity and mortality. We report a 12-year-old immunocompetent male child who was referred to the King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, in May 2010 after a sudden-onset headache and loss of consciousness. Brain imaging revealed a large right space-occupying occipital lesion and the patient underwent a craniotomy and resection. Histopathology of the lesion revealed necrotising granulomatous fungal encephalitis with many *hyphae* engulfed by multinucleated giant histiocytes. Two days later, a computed tomography scan showed debulking of the fungal mass and the patient was discharged on oral voriconazole. However, imaging at a six-week follow-up showed progression of the abnormality. A residual or persistent fungal brain lesion was suspected. Further neurosurgical resection of the lesion was performed and cultures showed growth of *Aspergillus flavus*. The patient was treated successfully with antifungal therapy over the following two years.

Keywords: Brain Abscess; Fungus Disease; *Aspergillus flavus*; Antifungal Agents; Immunocompetence; Case Report; Saudi Arabia.

المخلص: الرشاشيات داخل القحف الدماغية مظهر نادر للغاية من الرشاشيات الاجتياحية في الأطفال ذوي الكفاءة المناعية وتكون معدلات الاعتلال والوفيات نتيجة لذلك مرتفعة. نفيديكم بأن طفل بالغ من العمر 12 عاماً أُحيل إلى مستشفى الملك فيصل التخصصي ومركز الأبحاث في مايو 2010 حيث أن المريض أصيب بصداغ مفاجئ وفقدان للوعي. كشف تصوير الدماغ الأيمن آفة قذالي تحتل مساحة كبيرة وخضع المريض لاستئصال الآفة. وكشفت دراسة النسيج المستأصل بوجود التهاب دماغ فطري حبيبي تقرحي مع العديد من الخيوط المحاطة بمنسجات عملاقة متعددة النوى. بعد يومين، أظهر المسح المقطعي المحوسب خلو المخ من الكتلة الفطرية وخرج المريض على دواء فوريكونازول. ومع ذلك، أظهر التصوير المغناطيسي خلال ستة أسابيع تطور الفطريات في الدماغ مرة أخرى. تم تنفيذ مزيد من البتر للآفة في جراحة الأعصاب وأظهرت زراعة الانسجة نمو فطريات الفلافس. وتم علاج المريض بنجاح بالأدوية المضادة للفطريات على مدى العامين التاليين.

كلمات مفتاحية: خراج الدماغ؛ الأمراض الفطرية؛ ارشاشيات فلافس؛ الأدوية المضادة للفطريات؛ الكفاءة المناعية؛ تقرير حالة؛ العربية السعودية.

BRAIN ABSCESSES ARE A CHALLENGING emergency and any delay in diagnosis or treatment may result in poor health outcomes for affected patients. The incidence of this infectious disease is approximately 0.4–0.9 per 100,000 individuals worldwide, with much higher rates among immunocompromised patients.¹ Brain abscesses can be caused by bacteria, fungi or parasites.¹ *Aspergillus* sp. is an opportunistic ubiquitous fungus that usually enters the body by inhalation of airborne spores; it can then invade the central nervous system (CNS) via the haematogenous route, from direct extension through the paranasal sinuses or by direct inoculation during trauma or surgical procedures.^{2,3} Invasive intracranial aspergillosis is unusual, accounting for 10–20% of all

cases of invasive aspergillosis.⁴ Most patients with this condition have immune defects, usually in the form of neutrophil or macrophage dysfunction.^{5,6}

Invasive intracranial aspergillosis is associated with high morbidity and mortality rates; the latter can be as high as 88% in bone marrow transplant recipients and for those with disseminated or cerebral aspergillosis.^{2,7,8} CNS-invasive aspergillosis may present with meningitis, cerebritis, infarctions, abscesses, granulomas or mycotic aneurysms.⁹ The exact pathology depends upon the disease pathway and the host's immunity. The most frequent pathological findings are haemorrhage, infarctions and abscesses.¹⁰ Rarely, *Aspergillus* infections present as space-occupying lesions in immunocompetent patients.^{3,10}

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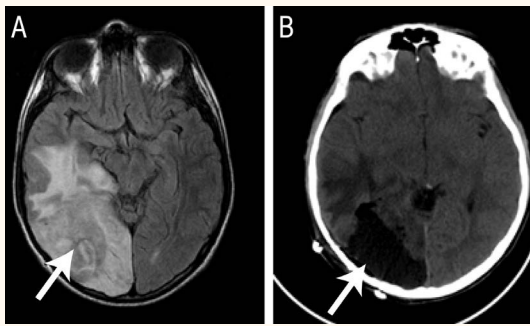


Figure 1A&B: A: Magnetic resonance imaging of the brain of a 12-year-old immunocompetent child showing a large right occipital mass (arrow) with heterogeneous enhancement, perilesional oedema in the right temporal and parietal lobes and a midline shift to the left. The nasal sinuses were clear. B: Post-resection computed tomography showing debulking of the right-sided occipital fungal mass (arrow) two days later. Note the regression of the perilesional reactive changes with a persistent mild midline shift to the left and regression of the right *trigone* effacement.

This report describes an invasive *Aspergillus*-induced brain abscess in an immunocompetent patient with no history of trauma.

Case Report

A previously healthy 12-year-old male child was referred to the King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, in May 2010 after a sudden-onset headache and loss of consciousness for 15 minutes. He had no convulsions, abnormal movements, eye abnormalities, vision impairment, fever, vomiting or skin rashes. In addition, he had no history of trauma. On examination, the patient was stable and interactive with no obvious neurological deficits. Computed tomography (CT) of the brain showed a right occipital space-occupying lesion, suspected to be a tumour. The nasal sinuses were clear. His complete blood count (haemoglobin: 135 g/L; white blood cell count: $6.4 \times 10^9/L$; neutrophil count: $2.51 \times 10^9/L$; eosinophils: $0.47 \times 10^9/L$; platelet count: $333 \times 10^9/L$) and erythrocyte sedimentation rate (3 mm/hour) were normal. Magnetic resonance imaging (MRI) of the brain revealed a large right occipital mass with heterogeneous enhancement and perilesional oedema in the right temporal and parietal lobes. The right occipital horn was compressed and there was a midline shift to the left [Figure 1A]. A preoperative diagnosis of a brain tumour was made.

The patient underwent a craniotomy and resection of the brain lesion. Histopathology examination of the lesion revealed necrotising granulomatous fungal encephalitis with many *hyphae* engulfed by multinucleated giant histiocytes. No cultures

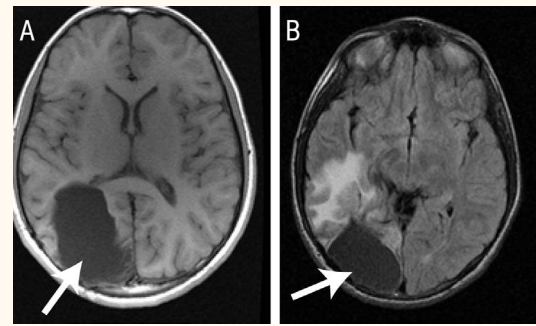


Figure 2A&B: A: Magnetic resonance imaging (MRI) of the brain of a 12-year-old immunocompetent child six weeks after an initial resection of a right occipital fungal mass showing progression of the dense solid marginal tissue abnormality (arrow) and enhancement consistent with a granulomatous tissue abnormality. B: Brain MRI one month after the second resection showing partial resolution of the solid parenchymal abnormality (arrow).

were requested as the lesion was believed to be a tumour. The patient was prescribed daily intravenous liposomal amphotericin B (5 mg/kg/dose). Two days after the surgery, a brain CT scan showed debulking of the right-sided occipital fungal mass. The extent of the perilesional reactive changes had regressed with a persistent mild midline shift to the left and regression of the right *trigone* effacement [Figure 1B]. Blood assays showed high (1,3)-beta-D-glucan levels (272 picogrammes [pg]/mL; normal range: 0–60 pg/mL) and non-reactive *Aspergillus* galactomannan. An eye examination, abdominal ultrasound and echocardiogram were unremarkable. The results of an immunological work-up were normal, including serum immunoglobulin levels, lymphocyte markers, blastogenic response, complement deficiency, oxidative burst and polymorphonuclear chemotaxis. A human immunodeficiency virus infection test was negative. The patient was discharged on oral voriconazole (6 mg/kg every 12 hours).

At a six-week follow-up appointment, the patient underwent CT and MRI scans of the brain which showed a progression of the dense solid marginal tissue abnormality. The enhancement was consistent with a granulomatous tissue abnormality [Figure 2A]. A residual or persistent fungal brain lesion was suspected and the patient subsequently underwent surgical exploration with further resection of the lesion. The histopathology remained consistent with that of the first resected brain lesion; however, cultures showed *A. flavus* growth. Oral administration of voriconazole was substituted for intravenous administration (6 mg/kg every 12 hours). Two days later, a postoperative CT scan showed a slight nonspecific enhancement in the periphery of the resected area. The patient was discharged with a prescription for oral voriconazole (6 mg/kg every 12 hours).

A one-month follow-up MRI scan of the patient showed resolution of the solid enhancing parenchymal abnormality [Figure 2B]. Subsequent MRI scans were performed at regular intervals, including four, six, 18 and 24 months after the second resection. After eight months of oral voriconazole treatment, (1,3)-beta-D-glucan levels were undetectable. Repeated assays for *Aspergillus* galactomannan also revealed undetectable levels. Antifungal treatment was discontinued after two years as there was on-going evidence of the complete resolution of the brain lesion by May 2013.

Discussion

In general, CNS aspergillosis—particularly invasive aspergillosis—is rarely observed in immunocompetent patients.² The brain is remarkably resistant to fungal infections due to its abundant blood supply and the relatively impermeable blood-brain barrier. Nevertheless, despite the existence of anatomical and functional barriers which protect the brain and subarachnoid space, fungal pathogens can breach these barriers under certain conditions.² Persistent cerebral *Aspergillus* abscesses in immunocompetent patients may exhibit clinical and radiological features similar to primary or secondary neoplasms or other forms of infection.¹⁰ Only a few cases of invasive *Aspergillus* brain abscesses have been reported; of these, most involved adult rather than paediatric patients.¹¹

The management of cerebral fungal abscesses remains controversial. Antifungal therapy alone reportedly has a poor outcome for patients with CNS aspergillosis, with a high mortality rate of >90%; this is likely due to the poor penetration of the CNS by the antifungal drugs.² Other research has indicated that surgical resection of focal CNS aspergillosis lesions reduces the mortality rate from 64% to 39%.² Overall, voriconazole seems to be the drug of choice for the treatment of aspergillosis.² In the current case, the patient showed clinical and radiological improvement with intravenous voriconazole administration and surgical resection. However, imaging scans at a six-week follow-up revealed that the lesion had progressed despite the continued administration of oral voriconazole; this is unusual due to the high bioavailability level (82.6%) of oral voriconazole.¹² This uncommon occurrence may have been due to poor medication compliance on the part of the patient or incomplete resection which resulted in the slow progression of the remnant lesion. Unfortunately, no facilities were available to monitor the patient's exact voriconazole drug levels.

In the current case, the patient had invasive CNS aspergillosis without paranasal sinus involvement and with no identifiable immune defects. Although he had negative *Aspergillus* serum galactomannan antigens, this negative result does not exclude a diagnosis of invasive aspergillosis.¹³ Culture supernatants of *A. flavus* have demonstrated lower reactivity, with lower galactomannan concentrations.¹⁴ Negative results could be due to factors related to the host, the assay or the fungus itself. One of the blood investigations which can be used to detect *Aspergillus* is the enzyme-linked immunosorbent assay Platelia™ *Aspergillus* EIA (Bio-Rad Laboratories, California, USA); this assay is most favourable in patients with haematological malignancies, especially those who have undergone a haematopoietic stem cell transplant and are neutropaenic.¹⁵

It is not clear how the patient in the present case developed the brain abscess. Although no immune defects were identified, he may nevertheless have been suffering from a rare form of immunodeficiency, such as an interleukin (IL)-4 or IL-6 deficiency; suppression of monocytes and T helper cells and interferon-gamma (IFN- γ) responses can lead to severe *Aspergillus* infections.^{13,16} A previous case report has indicated the beneficial role of IFN- γ treatment in combination with antifungal drugs in managing a patient with an *A. fumigatus*-induced brain abscess.¹⁷

Conclusion

Persistent cerebral *Aspergillus*-induced abscesses in immunocompetent patients are extremely rare and the clinical and radiological features of these cases may be similar to primary or secondary neoplasms or other forms of infection. Health professionals should therefore be aware of the symptoms of *Aspergillus*-induced brain abscesses, as early detection and appropriate treatment is necessary to ensure positive patient outcomes.

References

1. Brouwer MC, Tunkel AR, McKhann GM 2nd, van de Beek D. Brain abscess. *N Engl J Med* 2014; 371:447–56. doi: 10.1056/NEJMra1301635.
2. Chen S, Pu JL, Yu J, Zhang JM. Multiple *Aspergillus* cerebellar abscesses in a middle-aged female: Case report and literature review. *Int J Med Sci* 2011; 8:635–9. doi: 10.7150/ijms.8.635.
3. Köse S, Çavdar G, Senger SS, Akkoçlu G. Central nervous system aspergillosis in an immunocompetent patient. *J Infect Dev Ctries* 2011; 5:313–15. doi: 10.3855/jidc.1461.
4. Wannasirikul V, Chayakulkeeree M. Multiple brain abscesses caused by *Aspergillus fumigatus* in a patient with systemic lupus erythematosus. *J Infect Dis Antimicrob Agents* 2012; 29:17–20.

5. Sundaram C, Murthy JM. Intracranial *Aspergillus* granuloma. *Patholog Res Int* 2011; 2011:157320. doi: 10.4061/2011/157320.
6. Andrews T, Sullivan KE. Infections in patients with inherited defects in phagocytic function. *Clin Microbiol Rev* 2003; 16:597–621. doi: 10.1128/CMR.16.4.597-621.2003.
7. Mohindra S, Mukherjee KK, Chhabra R, Gupta SK, Gupta R, Kosla VK. Invasive intracranial aspergillosis: The management dilemmas. *Surg Neurol* 2008; 69:496–505. doi: 10.1016/j.surneu.2007.03.025.
8. Shamim MS, Enam SA, Ali R, Anwar S. Craniocerebral aspergillosis: A review of advances in diagnosis and management. *J Pak Med Assoc* 2010; 60:573–9.
9. Shuper A, Levitsky HI, Cornblath DR. Early invasive CNS aspergillosis: An easily missed diagnosis. *Neuroradiology* 1991; 33:183–5. doi: 10.1007/BF00588266.
10. Sidani C, Freiser ME, Saigal G, Sklar E. Unusual case of cerebral aspergillosis with clinical and imaging findings mimicking lymphoma. *Neuroradiol J* 2013; 26:290–6. doi: 10.1177/197140091302600306.
11. Dotis J, Iosifidis E, Roilides E. Central nervous system aspergillosis in children: A systematic review of reported cases. *Int J Infect Dis* 2007; 11:381–93. doi: 10.1016/j.ijid.2007.01.013.
12. Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. *Br J Clin Pharmacol* 2009; 68:906–15. doi: 10.1111/j.1365-2125.2009.03534.x.
13. Cenci E, Mencacci A, Casagrande A, Mosci P, Bistoni F, Romani L. Impaired antifungal effector activity but not inflammatory cell recruitment in interleukin-6-deficient mice with invasive pulmonary aspergillosis. *J Infect Dis* 2001; 184:610–17. doi: 10.1086/322793.
14. Verweij PE, Mennink-Kersten MA. Issues with galactomannan testing. *Med Mycol* 2006; 44:179–83. doi: 10.1080/13693786.2010.509744.
15. Dutkiewicz R, Hage CA. Aspergillus infections in the critically ill. *Proc Am Thorac Soc* 2010; 7:204–9. doi: 10.1513/pats.200906-050AL.
16. Monneret G, Venet F, Kullberg BJ, Netea MG. ICU-acquired immunosuppression and the risk for secondary fungal infections. *Med Mycol* 2011; 49:S17–23. doi: 10.3109/13693786.2010.509744.
17. Saulsbury FT. Successful treatment of *Aspergillus* brain abscess with itraconazole and interferon-gamma in a patient with chronic granulomatous disease. *Clin Infect Dis* 2001; 32:E137–9. doi: 10.1086/320158.