Received: 06.01.2010 / **Accepted:** 24.08.2010

DOI: 10.5137/1019-5149.JTN.2907-10.1

Treatment of Primary Aspergilloma of the Central Nervous System in a Diabetic Immunocompetent Patient with Surgical Resection and Voriconazole: A Case Report and Review of the Literature

Normal Bağışıklık Sistemine Sahip, Diyabetik Bir Hastada Santral Sinir Sisteminin Primer Aspergilloma'nın Cerrahi Olarak Çıkarılması ve Voriconazole ile Tedavisi: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Robin KOSHY, Prashant MALHOTRA

North Shore University Hospital, Division of Infectious Diseases, Manhasset, USA

Correspondence address: Prashant MALHOTRA / E-mail: pmalhotr@nshs.edu

ABSTRACT

Fungal infections of the central nervous system (CNS) are uncommon and occur mainly in immunocompromised patients. We describe a case of central nervous system aspergilloma without any evidence of systemic or paranasal foci in a diabetic but otherwise immunocompetent 71-year-old female treated successfully with surgical resection and medical therapy with voriconazole. Magnetic resonance imaging (MRI) after 6 months of voriconazole showed improvement and no evidence of residual or recurrent disease. Given its good CNS penetration, voriconazole along with surgical resection appears to be promising in treatment of these infections. Our case also demonstrates the importance of surgical intervention in the diagnosis and management of these atypical cases.

KEYWORDS: Aspergillus, Central nervous system, Voriconazole

ÖZ

Santral sinir sisteminde mantar infeksiyonları nadirdir ve esas olarak bağışıklık sistemi yetersizliği olan hastalarda görülür. Cerrahi olarak aspergilloması çıkarılmış ve voriconazole ille başarılı bir şekilde tedavi edilmiş, 71 yaşında bağışıklık sistemi yeterli diabetik erkek hasta olgusu bu yazıda sunulmaktadır. Manyetik rezonans görüntüleme incelemelerinde; voriconazole tedavisinden altı ay sonra nüks ya da artık (rezidüel) aspergilloma kalmadığı tesbit edilmiştir. Aspergilloma olgularında voriconazole'ün santral sinir sistemine iyi geçiş göstermesi nedeniyle cerrahi tedavinin yanı sıra kullanılması bu infeksiyonların tedavisinde ümit verici bir durumdur. Sunulan olgumuz atipik olguların tanı ve yönetiminde cerrahi yaklaşımın önemini vurgulamak açısından iyi bir örnektir.

ANAHTAR SÖZCÜKLER: Asperjillus, Merkezi sinir sistemi, Voriconazole

INTRODUCTION

Aspergillus is a common fungus that lives in the soil and decaying vegetation and is ubiquitous throughout the world (2). In general, these fungi are organisms of low pathogenicity, emerging as opportunistic organisms in a compromised host, however, infections in immunocompetent hosts have also been described (11).

The primary sites of infection are the lungs and the paranasal sinuses in immunosuppressed subjects though gastrointestinal and skin infection can occur. More rarely a central nervous system (CNS) primary infection can occur without an extracranial source with involvement of the cerebral parenchyma, the meninges or the vascular system (17).

Here we present a case of CNS aspergillosis in a diabetic but otherwise immunocompetent person with no other obvious extra cranial source, which was successfully treated with voriconazole after undergoing partial resection. This case illustrates the importance of obtaining biopsy specimens and surgical resection in conjunction with voriconazole in the management of these difficult to diagnose cases.

CASE REPORT

A 71-year-old Pakistani female was admitted to our hospital with new onset of seizures and headache. Her history

included type 2 diabetes mellitus, which was well controlled prior to admission. Examination was unrevealing with no focal deficits. Magnetic resonance imaging (MRI) of the brain showed a 3 cm right temporal enhancing mass (Figure 1,2). She underwent a stereotactic biopsy of the lesion. Pathology revealed fungal organisms with branching septate hyphae consistent with Aspergillus, cultures however remained negative. Voriconazole was started. Subsequently, she underwent partial resection of the lesion. Her workup for extra cranial source including CT and MRIs of sinuses, CT chest, a 2-dimensional echocardiogram and fungal blood cultures were negative. She was HIV negative and other than her diabetes had no immune compromise. She was treated with a 6-month course of voriconazole orally. Close clinical

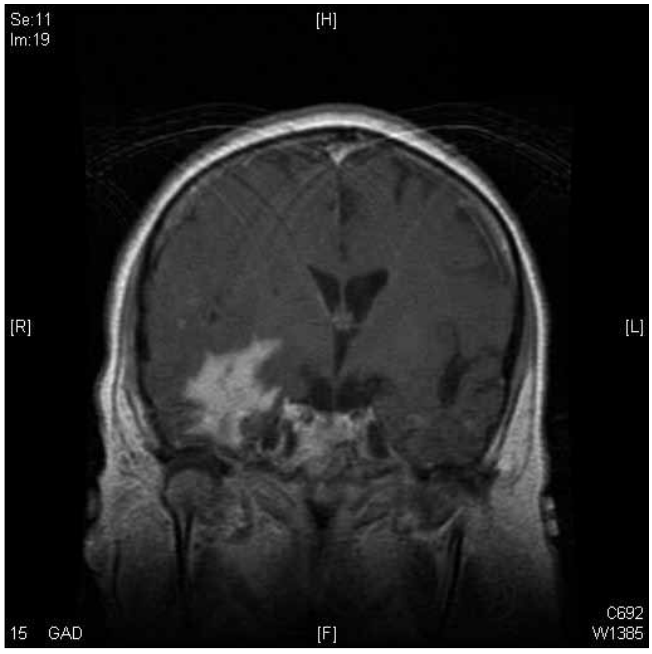

Figure 1: Coronal Post Gadolinium T1 weighted MRI showing Right temporal lobe lesion and surrounding edema.

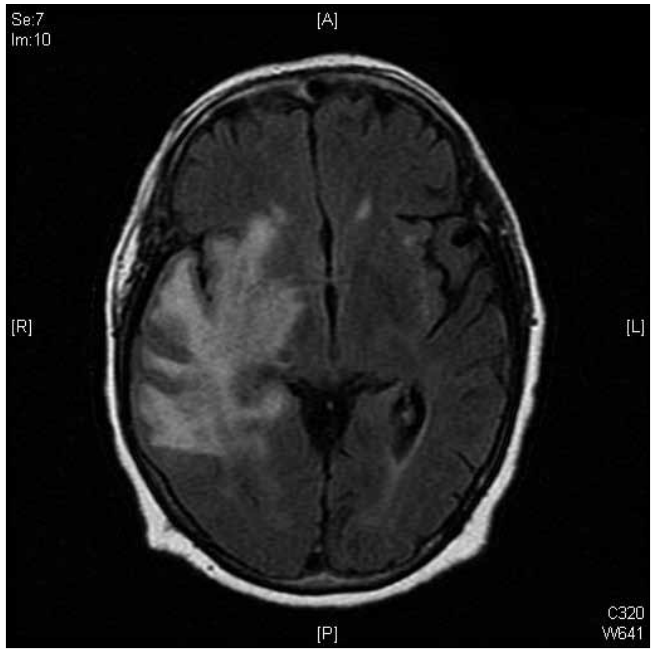

Figure 2: Axial Flare T 2 weighted MRI with water suppression showing Right basal ganglia/temporal lobe lesion

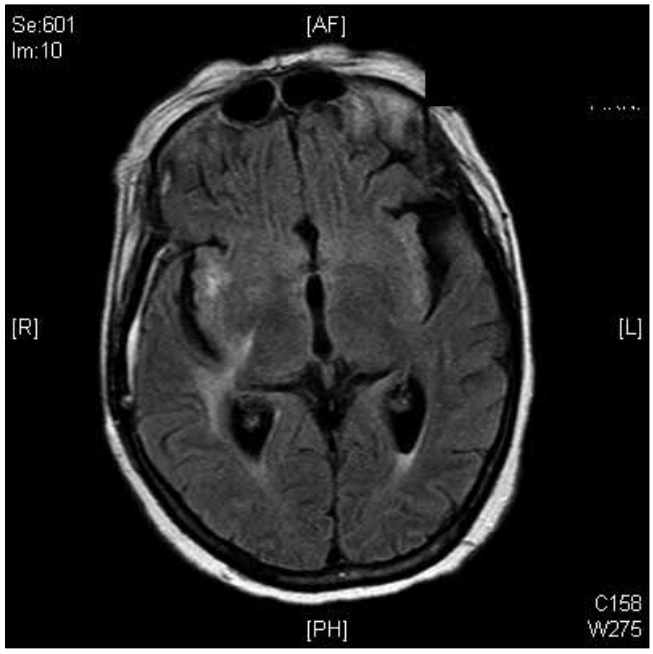

Figure 3: Axial flare T2 weighted MRI with water suppression 3 months into treatment showing improved Right basal ganglia/ temporal lobe lesion.

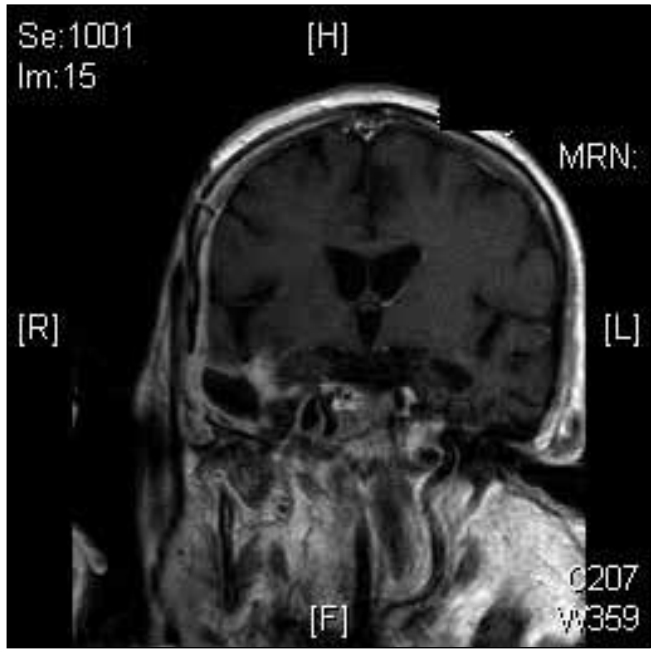

Figure 4: Coronal Post Gadolinium T1 weighted MRI 3 months into treatment demonstrating improved Right temporal lobe lesion.

and radiologic monitoring with serial MRIs (see Figure 3,4) did not reveal any evidence of residual or recurrent disease. At present, patient is doing well about 6 months after stopping therapy.

DISCUSSION

Central nervous system aspergillosis is an uncommon infection mainly occurring in the immunocompromised. It accounts for 5% of all intracranial fungal infections (24). It can manifest with acute onset of focal neurologic deficits. In those with paranasal disease, orbital involvement can be seen. Presenting symptoms include convulsions, fever, hemiparesis, cranial nerve deficits, paralysis and sensory impairment. Features of meningitis and subarachnoid hemorrhage resulting from mycotic aneurysms may occur (11,26).

Of late a newer class of patients have been recognized, those who are apparently immunocompetent, harboring CNS fungal infections. Case reports of atypical cases of aspergillosis in immuncompetent patients include vertebral osteomyelitis (26), skull base osteomyelitis (23), and infections of vascular grafts, have also been described (4).

Craniocerebral aspergillosis in immunocompetent hosts has been reported mainly from Pakistan, India, Saudi Arabia, Sudan, and other African countries (1,3,14,19). This prevalence in immunocompetent hosts is thought to be related to tropical hot and dry conditions, bad hygiene, and poor socioeconomic status (1,3,15). The mechanism causing invasiveness of aspergillosis in immunologically competent hosts remains unclear, but is thought to be unrecognized or poorly characterized qualitative cellular or sub cellular immunodeficiency (24). These cases present an interesting diagnostic dilemma for physicians and surgeons as the patient being immunocompetent, the possibility of fungal infection is considered low on the list of differentials. Surgical biopsy is therefore very important in establishing diagnosis.

The diagnosis of CNS aspergillosis can be aided by the use of cultures and neuroradiology. The characteristic findings of CNS disease are multiple infarctions or hemorrhages due to the angio-invasive nature of the fungus, particularly in immunocompromised patients. In immuncompetent individuals, the usual finding is a mass lesion with a thick irregular wall. The characteristic branching septate hyphae and conidia of Aspergillus species are seen on pathology (11).

Clinical outcomes in craniocerebral aspergillosis depend on the severity of the infective process and immune status of the patient (7,16) Mortality remains high and a case series from Pakistan of twenty-five immunocompetent patients with CNS aspergillosis showed an overall mortality of 28% when treated with itraconazole (22). Most case series recommend radical surgical excision followed by aggressive antifungal chemotherapy (1,7,19,25). In our patient, medical therapy in conjunction with surgical resection using voriconazole was successfully attempted.

Voriconazole is a broad-spectrum triazole that is active in vitro against various yeasts and molds, including Aspergillus species (9). Other antifungal agents including itraconazole, and caspofungin show negligible levels in cerebrospinal fluid or brain tissue (5,6,10,13). However, voriconazole has shown good penetration into the central nervous system in humans with a cerebrospinal fluid-to-plasma ratio of 0.22 to 1. In addition, high voriconazole brain tissue levels were found at autopsy in two patients with pulmonary aspergillosis, indicating that voriconazole is enriched in brain tissue (18). In a large randomized trial, initial therapy with voriconazole has shown superior efficacy compared to that with amphotericin B in all forms of invasive aspergillosis (12). Moreover, voriconazole has been used successfully in a few patients with CNS aspergillosis (8,20,21).

In immunocompetent hosts, mortality ranges from 40-80% (24). Patients with mainly sinonasal disease carry a good prognosis with mortality less than 20% and outcomes in extradural aspergillosis are better than intracerebral involvement (24).

To our knowledge this is one of the few documented cases of successful treatment of CNS aspergillosis in an otherwise immunocompetent patient with oral voriconazole after surgical resection. CNS aspergillosis should be considered a part of the differential in otherwise immunocompetent patients particularly from the tropical regions presenting with CNS lesions. Obtaining a biopsy is essential to diagnose these atypical cases. Our case also illustrates the importance of surgical resection in the treatment of these cases. Given its good CNS penetration, voriconazole therapy appears to be promising in treatment of these infections.

REFERENCES

1. Alrajhi AA, Enani M, Mahasin Z, Al-Omran K: Chronic invasive aspergillosis of the paranasal sinuses in immunocompetent hosts from Saudi Arabia. Am J Trop Med Hyg 65:83–86, 2001
2. Bennet JE: In: Harrison's Principles of Internal Medicine, 13th ed. Isselbacher KJ, Braunwald E, Wilson JD, editors. New York: Mc Graw Hill, 1995: 855, 861-862
3. Chugh KS, Sakhuja V, Jain S, Talwar P, Minz M, Joshi K, Indudhara R: High mortality in systemic fungal infections following renal transplantation in third-world countries. Nephrol Dial Transplant 8:168–172, 1993
4. Collazos J, Mayo J, Martinez E, Ibarra S: Prosthetic vascular graft infection due to Aspergillus species: Case report and literature review. Eur J Clin Microbiol Infect Dis 20: 414–417, 2001
5. Collette N, van der Auwera P, Lopez AP, Heymans C, Meunier F: Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericin B-deoxycholate. Antimicrob Agents Chemother 33:362-368, 1989
6. Collette N, van der Auwera P, Meunier F, Lambert C, Sculier JP, Coune A: Tissue distribution and bioactivity of amphotericin B administered in liposomes to cancer patients. J Antimicrob Chemother 27:535-548, 1991

7. Denning DW: Therapeutic outcome in invasive aspergillosis. Clin Infect Dis 23:608–615, 1996
8. Denning DW, Ribaud P, Milpied N, et al: Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 34:563-571, 2002
9. Espinel-Ingroff A: In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. J Clin Microbiol 39: 954-958, 2001
10. Hajdu R, Thompson R, Sundelof JG, et al: Preliminary animal pharmacokinetics of the parenteral antifungal agent MK-0991 (L-743,872). Antimicrob Agents Chemother 41: 2339-2344, 1997
11. Hall WA: Neurosurgical Infections in the Compromised Host in Haines SJ, Hall WA, eds. Neurosurgery Clinics of North America, Infections in Neurologic Surgery, Vol 3, Philadelphia: WB Saunders Co 1992:435-442
12. Herbrecht R, Denning DW, Patterson TF, et al: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408-415, 2002
13. Heykants J, Michiels M, Meuldermans W, et al: The pharmacokinetics of itraconazole in animals and man: an overview. In: Fromtling RA, ed. Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. Barcelona: J.R. Prous Science Publishers, 1987:223-249
14. Hussain S, Salahuddin N, Ahmad I, Salahuddin I, Jooma R: Rhinocerebral invasive mycosis: Occurrence in immunocompetent individuals. Eur J Radiol 20:151–155, 1995
15. Kameswaran M, al-Wadei A, Khurana P, Okafor BC: Rhinocerebral aspergillosis. J Laryngol Otol 106:981–985, 1992
16. Kim DG, Hong SC, Kim HJ, Chi JG, Han MH, Choi KS, Han H: Cerebral aspergillosis in immunologically competent patients. Surg Neurol 40:326–331, 1993
17. Kleinschmidt-DeMasters BK: Central nervous system aspergillosis: A 20- year retrospective series. Hum Pathol 33: 116-124, 2002
18. Lutsar I, Roffey S, Troke P: Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis 37:728-732, 2003
19. Murthy JM, Sundaram C, Prasad VS, Purohit AK, Rammurti S, Laxmi V: Aspergillosis of central nervous system: A study of 21 patients seen in a university hospital in South India. J Assoc Physicians India 48:677–681, 2000
20. Perfect JR, Marr KA, Walsh TJ, et al: Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 36:1122-1131, 2003
21. Schwartz S, Milatovic D, Thiel E: Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. Br J Haematol 97:663-665, 1997
22. Sharma RR, Lad SD, Desai AP, Lynch PG: Surgical management of fungal infections of the nervous systems. In: Schmidek HH, ed. Schmidek and Sweet Operative Neurosurgical Techniques: Indications, Methods and Results, 4th ed. Philadelphia: WB Saunders Company, 2000:1726-1755
23. Shelton SC, Antonelli PJ, Hackett R: Skull base fungal osteomyelitis in an immunocompetent host. Otolaryngology–Head and Neck Surgery 126: 76-78, 2002
24. Siddiqui AA, Shah AA, Bashir SH: Craniocerebral Aspergillosis of sinonasal origin in immunocompetent patients: Clinical spectrum and outcome in 25 cases. Neurosurgery 55: 602-613, 2004
25. Steinbach WJ, Stevens DA, Denning DA: Combination and sequential antifungal therapy for invasive aspergillosis: Review of published in vitro and in vivo interactions and 6281 clinical cases from 1966 to 2001. Clin Infect Dis 37 [Suppl 3]: S188–S224, 2003
26. Vinas FC, King PK, Diaz FG: Spinal Aspergillus osteomyelitis. Clin Infect Dis 28: 1223–1229, 1999