

İnvazif Aspergilloza Bağlı Orbital Apeks Sendromu Olan Renal Transplant Alıcısı

A Renal Transplant Recipient With Orbital Apex Syndrome Due to Invasive Aspergillosis

Serkan Yener¹, Ali Çelik², Dilek Tekiş¹, Semih Sütay³, Süleyman Kaynak⁴, Nusret Yılmaz¹, Caner Çavdar², Taner Çamsarı²

¹Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir

²Dokuz Eylül University Faculty of Medicine, Department of Nephrology, İzmir

³Dokuz Eylül University Faculty of Medicine, Department of Otolaryngorhinology, İzmir

⁴Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir

ÖZET

Renal transplantasyon sonrası 2. ayda gelişen sol gözde görme bozukluğu nedeniyle değerlendirilen hastada 3, 4 ve 6. kranial sinir tutulumu ve orbital apeks sendromu saptanmış ve yapılan ileri tetkiklerde sol etmoid ve sfenoid sinüslerde akut inflamasyon saptanmıştır. Paranasal sinüs endoskopisi ve biyopsi sonuçları hastada invazif aspergilloz sinüziti olduğunu göstermiştir. Kranial ve orbital manyetik rezonans görüntülemeleri de inflamasyonun orbital apekse, kavernöz sinüse ve internal karotis arterine yayıldığını göstermiştir. Hasta 56 gün boyunca lipozomal amfoterisin B ile tedavi edilmiş, ve idame tedavisinde günlük 200 mg itraconazol kullanılmıştır. Hastada bu tedavi ile belirgin düzelleme saptanmıştır. Hasta şu anda sağlıklı olarak hemodiyaliz programında izlenmektedir.

Anahtar sözcükler: transplantasyon, orbital apeks sendromu, aspergilloz

ABSTRACT

A Turkish patient was evaluated because of loss of vision of the left eye at the second month after renal transplantation. The ophthalmologic examination showed the involvement of IIIrd, IVth and Vth cranial nerves and orbital apex syndrome was diagnosed. Further investigations showed the presence of acute inflammation in left ethmoid and sphenoid paranasal sinuses. The results of the paranasal sinus endoscopy and pathological examination of the punch biopsies were consistent with invasive aspergillosis sinusitis. Cranial and orbital magnetic resonance images showed orbital cellulitis with the involvement of orbital apex. There was also cavernous sinus thrombosis and thrombosis of internal carotid arteria. The patient was treated with liposomal amphotericin B for 56 days and with itraconazole 200 mg/day for the maintenance therapy. A significant regression of the invasive sinusitis was achieved with this therapy. The patient is now on haemodialysis with good health.

Keywords: transplant, orbital apex syndrome, aspergillosis

2005;14 (4) 205-207

Introduction

Systemic fungal infections are important problems for immunocompromised renal transplant recipients (1). The incidence of fungal infections ranges between 0-14% in kidney recipients. Aspergillosis is the second frequent fungal infection complicating solid organ transplantation (2). Orbital apex syndrome is as-

sociated with the involvement of IIInd, IIIrd, IVth and Vth cranial nerves due to orbital lesions such as neoplasms, haemorrhages or inflammations. Orbital aspergillosis is a relatively uncommon orbital infection, usually seen in immunocompromised individuals (3). Orbital apex syndrome due to aspergillus sphenoid sinusitis is a rare condition. We report a favourable outcome in a renal transplant recipient with invasive aspergillosis presenting with orbital apex syndrome.

Case Report

A 53-year-old Turkish male patient with end-stage renal failure secondary to polycystic kidney disease re-

Yazışma adresi: Dr. Serkan Yener

Dokuz Eylül Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, 35340, Inciraltı, İzmir

Tel: 0 (232) 412 3701

E-posta: syener@deu.edu.tr

ceived a cadaveric 2 antigen matched renal allograft from marginal donor in June 2002. The initial immunosuppressive regimen included prednisolone (40 mg/day), mycophenolate mofetil (MMF) (1000 mg/day) and antithymocyte globulin (ATG) (150 mg/day for 12 days). The early postoperative course was complicated by acute tubular necrosis (ATN) and the patient was put on hemodialysis three times during the following eleven days. The patient was discharged with serum creatinine stabilized at 2.5 mg/dL with the immunosuppressive regimen including 25 mg/day prednisolone, 1500 mg/day MMF and 150 mg/day cyclosporine-A. The prophylactic antimicrobial regimen included oral nystatin, trimethoprim-sulfamethoxazole and ganciclovir. Ganciclovir 2.5 mg/kg IV twice daily was used for 12 days during ATG treatment.

At the second month the patient presented with headache, rapid loss of vision and ptosis at the left eye. The left eye was anisocoric and had no response to light. Eye movements to all directions were restricted. Third, IVth and VIth cranial nerves were thought to be involved. There were no other neurological findings. These signs were related with the involvement of optic foramen and superior orbital fissure and revealed the presence of "orbital apex syndrome". Cranial and orbital MRI-scans showed acute inflammatory changes in left ethmoid and sphenoid sinuses, orbital cellulitis with the involvement of orbital apex. There was also cavernous sinus thrombosis and thrombosis of internal carotid artery (ACI). Paranasal sinus endoscopies showed the involvement of the left sphenoid sinus with bone destruction. Punch biopsies were taken from sphenoid and ethmoid sinuses.

Anti-edema therapy with mannitol and heparin were started. Liposomal amphotericin B 3 mg/kg/day was started empirically. MMF and cyclosporine were stopped and prednisolone was tapered to 10 mg/day. The pathological diagnosis was aspergillosis (*Aspergillus niger*) of the left sphenoid sinus. Amphotericin B was continued but debridement of the necrotic tissues were not performed in order to prevent the dissemination of the infection to the cerebrospinal fluid.

At the 3rd week of the therapy orbital and cranial MRI were repeated. No progression was determined. The patient was treated with liposomal amphotericin B for 56 days. Prednisolone dose was tapered to 5 mg/day gradually in eight weeks. The patient was discharged with prednisolone 5 mg/day, warfarine and itraconazole 200 mg/day. Haemodialysis was started two months after the cessation of the immuno-

suppressive therapy.

Repeated eye and paranasal sinus examinations and cerebral and orbital MRI scans did not show any evidence of re-infection or progression since discharge. The patient has been in good health for 36 months.

Discussion

Fungal infections are serious complications following solid organ transplantations. The incidence of fungal infections ranges between 0-14% in kidney recipients. Aspergillosis is the second frequent fungal infection in solid organ transplantation recipients (3). Lin et al, in their meta-analysis including clinical trials between 1995-2000, showed that 21 (8%) of 252 solid organ transplant recipients with aspergillosis were kidney transplant recipients (4). *Aspergillus* infections in organ transplant recipients occur usually between the 1st and 3rd months after transplantation (5). The most common species of *Aspergillus* causing invasive diseases are *A. fumigatus*, *A. flavus* and *A. niger* (6). The definitive diagnosis requires histologic demonstration of typical hyphae in tissue and positive culture test (1,6). Punch biopsies taken from sphenoid and ethmoid sinuses showed the presence of invasive aspergillosis in our patient.

Risk factors for invasive aspergillosis include ATG/OKT3 therapy, history of steroid boluses, history of systemic infections (CMV, pneumoniae, sepsis, etc.), cyclosporin, MMF and prolonged use of antibiotics (2,7). Most of these were present in our patient.

Aspergillosis of the paranasal sinus may present as allergic, non-invasive, invasive and fulminant. Panda et al offered to use the term "fulminant aspergillosis" for paranasal sinus aspergillosis if tissue invasion and vascular invasion is present (8). Orbital aspergillosis is a relatively uncommon orbital infection, usually seen in immunocompromised individuals. The paranasal sinuses are the usual portal of entry for the organism, with orbital extension more likely when host defences are impaired (3). Orbital apex syndrome due to aspergillus sphenoid sinusitis is a rare condition (9).

Available and effective anti-fungal drugs against aspergillosis are amphotericin B, caspofungin, voriconazole and itraconazole. Liposomal amphotericin B with less toxicity than the standard formulation (amphotericin B deoxycholate) can be used 1-5 mg/kg/day in invasive aspergillosis (6). Caspofungin is a new antifungal agent with *in vitro* activity against candida and aspergillus. Despite the lack of enough evidence about

the effectiveness of caspofungin in invasive aspergillosis, favourable results were noted in the refractory aspergillosis (10). Voriconazole is a wide spectrum triazole antifungal agent with efficacy against aspergillosis (11,12). Itraconazole is an important option in the management of invasive aspergillosis. The compound has *in vitro* potent and broad-spectrum antifungal activity against aspergillus spp. with a species and strain dependent fungicidal mode of action. However, the experience with itraconazole for induction therapy of invasive aspergillosis is limited. Itraconazole has an important role for consolidation and maintenance therapy of patients with invasive aspergillosis (13). Itraconazole was used for the maintenance therapy in our patient.

Physicians must be aware of invasive fungal infections of the paranasal sinus and orbita in immunosuppressed patients who present with acute onset of headache, visual problems and fever. If the tissue invasion is confirmed, empirical antifungal therapy must be initiated without delay.

References

1. Koselj-Kajtna M, et al. Aspergillus infection in immunocompromised patients. *Transplant Proc* 2001; 33(3): 2176-8.
2. Paya CV. Fungal infections in solid-organ transplantation. *Clin Infect Dis* 1993; 16(5): 677-88.
3. Levin LA, et al. The spectrum of orbital aspergillosis: a clinicopathological review. *Surv Ophthalmol* 1996; 41(2): 142-54.
4. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; 32(3): 358-66.
5. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; 338(24): 1741-51.
6. Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998; 26(4): 781-803; quiz 804-5.
7. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. *Rev Infect Dis* 1990; 12(6): 1147-201.
8. Panda NK, et al. Paranasal sinus aspergillosis: its categorization to develop a treatment protocol. *Mycoses* 2004; 47(7): 277-83.
9. Lee LR, Sullivan TJ. Aspergillus sphenoid sinusitis-induced orbital apex syndrome in HIV infection. *Aust N Z J Ophthalmol*, 1995; 23(4): 327-31.
10. Klastersky J. Empirical antifungal therapy. *Int J Antimicrob Agents* 2004; 23(2): 105-12.
11. Denning DW, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; 34(5): 563-71.
12. Herbrecht R, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347(6): 408-15.
13. Groll AH. Itraconazole—perspectives for the management of invasive aspergillosis. *Mycoses* 2002; 45 Suppl 3: 48-55.