Successful Treatment of Deep Cutaneous Zygomycosis Developing Early After Renal Transplantation

Böbrek Nakli Sonrası Gelişen Subkutanöz Zigomikoz Enfeksiyonunun Başarılı Bir Şekilde Tedavisi

ABSTRACT

A 25-year-old male patient with end-stage renal disease due to chronic pyelonephritis who had undergone renal transplantation was admitted 20 days after the operation with complaints of nausea, vomiting and darkening in the skin of the transplantation site. A 30x30 cm area of skin at the transplantation site in the left inguinal area was dark colored and of necrotic appearance. Gram-negative and gram-positive bacilli were observed in the gram stain of the material taken from the lesion through thin needle aspiration. Surgical debridement of necrotic tissues at the lesion site was performed. There were fungi with bacterial groups and branched rough hyphae infiltrating the necrotic lipid and connective tissue. The venous wall was under the invasion of these fungi hyphae in the histopathological examination of the debridement material and a diagnosis of subcutaneous zygomycosis was established. Amphotericin B was administered for 14 days at a cumulative dose of 625 mg. The skin defect at the left lower quadrant was closed by placing a graft. The patient no longer required dialysis after two weeks of hospitalization. He was discharged 48 days later with total recovery of the lesion site and a serum creatinin level of 2 mg/dL, under treatment with cyclosporine 400 mg/day and prednisolone 20 mg/day.

KEY WORDS: Renal transplantation, Wound infection, Zygomycosis, Recovery

ÖZ

Kronik pyelonefrite bağlı son dönem böbrek yetmezliği nedeniyle renal transplantasyon yapılmış 35 yaşındaki erkek hasta, operasyondan 20 gün sonra mide bulantısı, kusma, transplantasyon bölgesi derisinde esmerleşme ile başvurdu. Sol inguinal bölgede, transplant sahasında 30x30cm'lik bölgede deride nekrotik görünümlü kararma görüldü. İnce iğne aspirasyonu ile alınan materyalin gram boyamasında gram negatif ve gram pozitif basil izlendi. Daha sonra nekrotik doku debritmanı yapıldı ve nekrotik yağ ve bağ dokusunu infiltre eden mantar ile birlikte bakteri kolonizasyonu ve dallı hifalar görüldü. Debritman materyalinden yapılan histopatolojik incelemede mantar hifalarının invazyon yerinin altında venöz duvarın görülmesiyle subkutanöz zygomycosis tanısı konuldu. 14 gün boyunca kümülatif olarak 625 mg Amfoterisin B tedavisi verildi. Sol alt kadrandaki deri defekti de greft ile kapatıldı. Hasta 2 hafta hastanede yattıktan sonra diyaliz tedavisine ihtiyacı kalmadı. Hasta lezyon sahasının tamamen iyileşmesinden 48 gün sonra, 400 mg/gün siklosporin ve 20 mg/gün prednizolon tedavisi ile kreatinin seviyesi 2 mg/dL düzeyine gelince taburcu edildi.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Enfeksiyon, Zigomikoz, İyileşme

Bülent TOKGÖZ[1]
İsmail KOÇYİĞİT[1]
Orhan YILDIZ[2]
Aydın ÜNAL[1]
Murat H. SİPAHİOĞLU[1]
Atilla ÇORUH[3]
Işın SOYUER[4]
Oktay OYMAK[1]
Cengiz UTAŞ[1]

1 Erciyes University, Faculty of Medicine, Department of Nephrology, Kayseri, Turkey
2 Erciyes University, Faculty of Medicine, Infectious Diseases and Clinical Microbiology Department, Kayseri, Turkey
3 Erciyes University, Faculty of Medicine, Department of Plastic Surgery, Kayseri, Turkey
4 Erciyes University, Faculty of Medicine, Department of Pathology, Kayseri, Turkey

Received : 13.06.2010
Accepted : 02.12.2010

Correspondence Address:
Bülent TOKGÖZ
Erciyes Üniversitesi Tıp Fakültesi,
Nefroloji Bilim Dalı,
Kayseri, Turkey
Phone : +90 352 437 93 49
Fax : +90 352 437 58 07
Gsm : +90 533 732 79 88
E-mail : bulentto@gmail.com

INTRODUCTION

Post-transplantation skin infections should be carefully evaluated as they might indicate systemic infection due to opportunistic pathogens. A tissue biopsy may be absolutely necessary for the diagnosis since immunosuppressive therapy may lead to diagnostic difficulties by changing the symptoms. One of the skin infections seen in these patients is zygomycosis due to fungi of the *Zygomycetes* class, *Mucorales* group, *Mucoraceae* family commonly found in nature. Zygomycosis is observed more often in patients whose immune systems are suppressed, and it may have an acute and fulminant course of progression (1, 2). Although *Rhizopus arrhizus* has been reported as the most frequent cause in human zygomycosis, many other pathogens may constitute factors for infection in humans (1, 3). Zygomycosis may lead to diffuse disease, or it may be limited to the peritoneal, pelvic, rhinocerebral, pulmonary or dermal area (1).

In this report, we present a case in which graft insufficiency and cutaneous zygomycosis that developed early after renal transplantation were successfully treated.

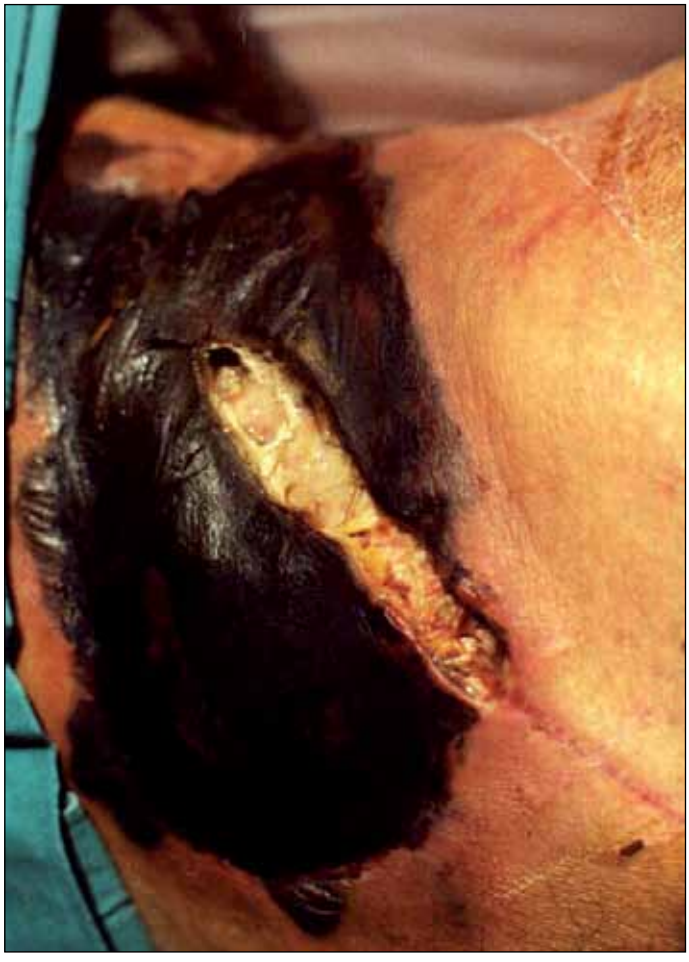

Figure 1: *Dark colored necrotic tissue at the transplantation site.*

CASE REPORT

A 25-year-old male patient with end-stage renal disease due to chronic pyelonephritis who had undergone renal transplantation from a living nonrelated donor was admitted to our clinic 20 days after the operation with complaints of nausea, vomiting and darkening in the skin of the transplantation site. He had been receiving an immunosuppressive regimen of steroid and cyclosporine since the transplantation. His medical history revealed that he had his first renal transplantation from his mother 30 months previously. However, his transplanted kidney was exposed to renal biopsy three times due to varying degrees of graft insufficiency. He had received at least two acute rejection treatments in his first renal transplantation and returned to dialysis therapy at the end of the second year.

His blood pressure was 130/80 mm Hg, pulse rate 100/min, and temperature 36.6 °C. A 30x30 cm of the skin at the transplantation site in the left inguinal area had a dark-colored necrotic appearance, the incision line seemed to be open, and there was a slight purulent discharge (Figure 1).

Laboratory analysis revealed hemoglobin: 7.7 g/dL, white blood cells: 7800/mm^3, thrombocytes: 110000/mm^3, blood urea nitrogen: 222 mg/dL, creatinin: 20.7 mg/dL, sodium: 123 meq/L, and potassium: 4.8 meq/L. Microscopic analysis of the urine revealed no findings except 10-12 erythrocytes in each of the high-powered fields. In the gram stain, gram-negative and gram-positive bacilli were observed in the material taken from the lesion through thin needle aspiration. The cyclosporine level (C_2) was measured as 847 μg/mL.

The patient was immediately given bicarbonated hemodialysis with the indication of acute dialysis. After samples were collected for aerobic and anaerobic cultures, empirical antibiotic treatment was started with ciprofloxacin and clindamycin. Immunosuppression was decreased to 200 mg/day, to azathioprine 100 mg/day and prednisolone 50 mg/day. A biopsy taken from the transplanted kidney within 24 hours revealed acute rejection in a very early period. When thin needle-aspirated *Pseudomonas aeruginosa* grew in the culture, clindamycin was discontinued and netilmycin added at a dose of 50 mg/36 hours. Surgical debridement of necrotic tissues at the lesion site was performed, and the debridement material was sent for histopathological examination. The histopathological examination revealed that there were fungi with bacterial groups and branched rough hyphae infiltrating the necrotic lipid and connective tissue. In addition the venous wall was under invasion by these fungal hyphae (Figure 2), and a subcutaneous zygomycosis diagnosis was established. On the 15th day of his hospitalization he was started on amphotericin B for 14 days at a cumulative dose of 625 mg. Daily dressing of the lesion continued. During the period of monitoring his renal function gradually improved, and the amount of urine increased to 3000-5000 ml. On the 28th day of his hospitalization, azathioprine

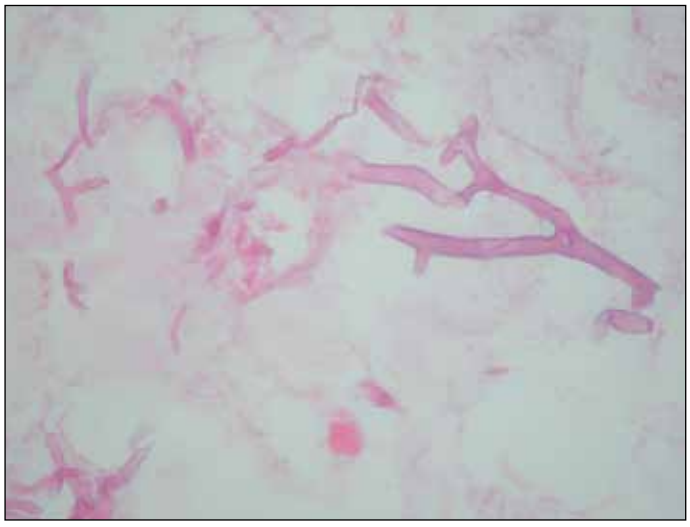

Figure 2: *Branched rough hyphae infiltrating necrotic tissue.*

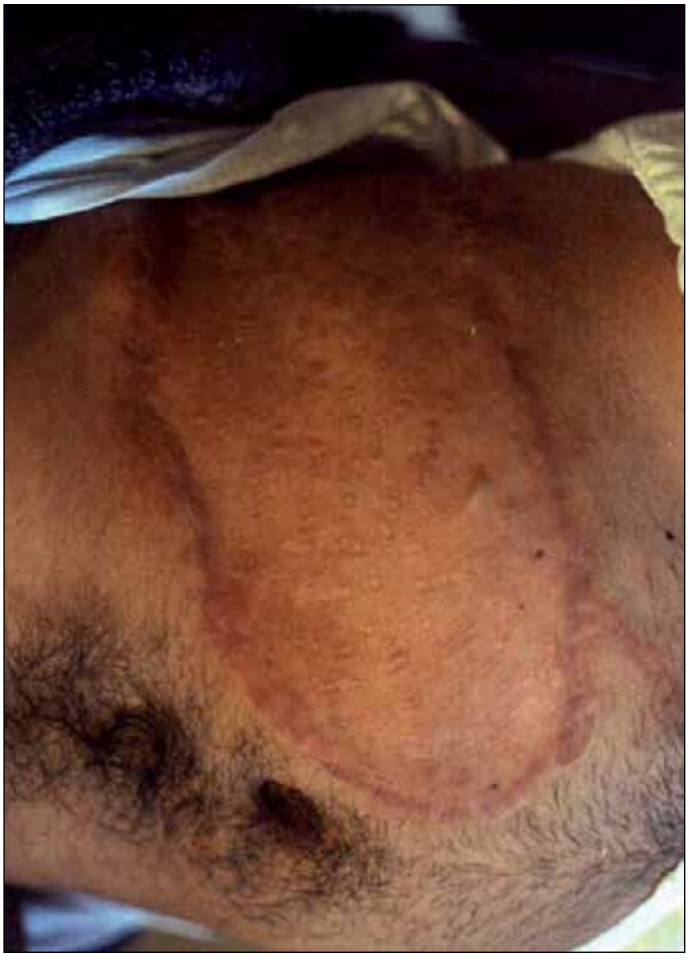

Figure 3: *Total recovery of the lesion site.*

treatment was discontinued due to leukopenia. The presence of recurrent *Pseudomonas aeroginosa* proliferation in spite of suitable antimicrobial treatment was evaluated as clinically unresponsive, and ciprofloxacin was discontinued. Treatment was continued with meropenem and netilmycin for 14 days. On the 32nd day of his hospitalization, the skin defect at the left lower quadrant was closed by placing a graft. After two weeks of hospitalization, he did not require any dialysis. On the 48th day of his hospitalization, the patient was discharged with total recovery of the lesion site (Figure 3) and a serum creatinin level 2 mg/dL while under treatment with cyclosporine 400 mg/day and prednisolone 20 mg/day. The patient is still being followed up regularly and his creatinine level ranges from 1.3 to 1.7 mg/dL.

DISCUSSION

Despite all the improvements achieved in organ transplantation, infections that may develop as a result of immunosuppression still lead to severe morbidity and mortality. The first six months of transplantation is the period in which immunosuppression is most intensive. Infections that develop during this period may reveal findings demonstrating unexpectedly different and opportunistic pathogens.

Skin infections that develop early in the post-transplantation period appear after due to catheter, lung and urinary system infections with respect to their prevalence. Fungi have rarely played a role in the etiology. Although fungal skin reactions are generally limited, they should be carefully evaluated since they may indicate a systemic infection and/or present a risk for rapid spread. Diagnostic difficulties usually require tissue biopsy.

In the above-presented case, the diagnosis of zygomycosis was established by histopathological examination because the discharge obtained from the lesion could not be isolated from the aspirate and tissue cultures. It is known that the primary microorganism is difficult to identify in a culture. Reviewing known cases revealed that the diagnosis was based on biopsy examination in most of cases, and attempts to reproduce it in the culture failed (4,5). As far as we know, culture was successful in only two cases, with *Apophysomyces elegans* isolated in one and *Cunninghamella bertholletiae* in the other (6-8).

Microorganisms belonging to the family of *Zygomycetes* which can potentially cause infections in humans, are not found in normal human flora but can be found almost everywhere in nature (1,8). Nosocomial transmission has been known (1). Microorganisms that enter into the body through inhalation, direct contact or ingesting of foods with spores may lead to colonization or to invasive diseases only if the immune system is suppressed (1,7,8).

In contrast to other infections, localization of zygomycosis cutaneous involvement is rarely related to severe systemic infections, and local factors facilitating colonization such as burns, trauma, and pinpricks have been suggested (3).

In a transplant recipient, atypical mycobacteria, fungi, even algae can be identified as the agents causing localized skin infections (9). It has been reported that fungal infections develop at a rate proportional to the amount of rejection therapy received

by the patients of renal transplantation (10). Similar to Candida infections, *Zygomycetes* infections may demonstrate systemic spread after skin infections.

Although there have been a number of articles on the development of zygomycosis in transplant recipients (1, 3-6, 8, 11, 12), a limited number of cases with cutaneous zygomycosis have been reported to date (6,13,14). The above-mentioned case of cutaneous zygomycosis identified in a renal transplant recipient has become the fifth case after four previously reported cutaneous zygomycosis cases (6,13,14). The rate of skin infection among other zygomycosis localizations was reported to be 16%. Nampoory *et al*. found the incidence of fungal infections to be 3.5% in their retrospective review of 512 renal transplant recipients (11). In this study, the number of zygomycosis cases followed the number of cases of candidiasis, aspergillosis and cryptococcus infections. In the study by Nampoory *et al*., only two cases of zygomycosis were identified among 512 patients; one of them involved the lungs, and the other involved the allograft itself; however, cutaneous involvement was not reported (11).

The remarkable dark necrotic appearance in this case presented here was also identified by Adriaenssens *et al*. who recently reported a case with established cutaneous mucormycosis as seen with a dark necrotic skin lesion (12).

Jimenez *et al*. reported five successfully treated mucormycosis cases, in whom the infection had developed after liver and pancreas-kidney transplantation (5). In this study, cutaneous infection was identified in two of the five cases; and diabetes mellitus was present as a risk factor either before the transplantation, or it developed in the post-transplantation period in all of the cases involved. The cases received at least one intensive immunosuppressive treatment due to acute rejection (5). The diagnosis was established either on the basis of the findings in culture or of the biopsy, and liposomal amphotericin B was administered as an adjunct treatment beside surgical resection. Naguip *et al*. isolated *Apophysomyces elegans* in a renal transplant patient as the agent causing skin infection developed from trauma (6).

Zygomycosis generally has an acute fulminant progression in immunosuppressed patients (1). The rate of mortality due to cutaneous zygomycosis has been reported to be approximately 16% (3). In contrast, the rates of mortality in cases of rhinocerebral and pulmonary affliction and disseminated conditions were, respectively, 67%, 83%, and 100%.

The administered dose of amphotericin B was high (0.5 mg/kg/day) in the present case since the estimated creatinine clearance was below 10 ml/min. There is no consensus on the duration of anti-fungal treatment for *Zygomycetes* infections. Long-term treatments of 6-8 weeks are generally recommended. Treatment was discontinued on the 14th day in the present case since the surgical debridement of the necrotic tissues was complete and the locus of infection together with the dead tissues was removed completely. Duration of treatment was short because cutaneous infection in zygomycosis rarely leads to severe systemic infection in contrast to other localizations. Although the onset of anti-fungal treatment was delayed for 15 days, the patient was treated successfully. Obviously early and effective surgical debridement is more important than anti-fungal treatment. Surgical treatment consisted of the excision of the eschar of 30x30 cm size localized on the left lower quadrant of the abdominal wall down to the deep fascia. The defect was reconstructed with a split-thickness skin graft a week after the debridement. The graft healed uneventfully without any complications.

In conclusion, invasive fungal infections still constitute significant causes of morbidity and mortality in renal transplant recipients. Early establishment of the diagnosis and initiating appropriate treatment is necessary in cases with disseminated infections, taking into account the high risk for mortality (up to 100%). *Zygomycetes* infections may develop during surgical operations, as a result of trauma or during catheter placement. Therefore, particular attention should be diverted to the protection of the skin of the transplant patient. The case that constitutes the subject of the present paper demonstrated once more that a rapid and intensive treatment approach is effective against opportunistic infections in renal transplant recipients.

REFERENCES

1. Rinaldi MG: Zygomycosis. Inf Dis Clin North Am 1989; 3: 19-41
2. Utas C, Unluhizarci K, Okten T, Unlu Y, Doganay M, Kelestimur F: Acute renal failure associated with rhinosinuso-orbital mucormycosis infection in a patient with diabetic nephropathy. Nephron 1995; 71: 235
3. Adam RD, Hunter G, DiTomasso J, Comerci G: Mucormycosis:Emerging prominence of cutaneous infection. Clin Inf Dis 1994; 19: 67-76
4. Martinez EJ, Cancio MR, Sinnott JT, Vincent AL, Brantley SG: Nonfatal gastric mucormycosis in a renal transplant recipient. South Med J 1997; 90: 341-344
5. Jimenez C, Lumbreras C, Aguado JM, Loinaz C, Paseiro G, Andres A, Morales LM, Sanchez G, Garcia I, del Placio A, Moreno E: Succesful treatment of mucor infection after liver or pancreas-kidney transplantation. Transplantation 2002; 73: 476-480
6. Naguip MT, Huycke MM, Pederson JA, Pennington LR, Burton ME, Greenfield RA: Apophysomyces elegans infection in a renal transplant recipient. Am J Kidney Dis 1995; 26: 381-384
7. Lehrer RL, Howard DH, Sypherd PS, Edwards JE, Segal GP, Winston DJ: Mucormycosis. Ann Intern Med 1980; 93: 93-108
8. Zhang R, Zhang JW, Szerlip HM: Endocarditis and hemorrhagic stroke caused by Cunninghamella bertholletiae infection after kidney transplantation. Am J Kidney Dis 2002; 40: 842-846

9. Sia IG, Paya CV: Infectious complications following renal transplantation. Surg Clin North Am 1998; 78: 95-112
10. Haim S, Better OS, Lichtig C, Erlik D, Barzilai A: Rhinocerebral mucormycosis following kidney transplantation. Isr J Med Sci 1970; 6: 646-649
11. Nampoory MR, Khan ZU, Johny KV, Constandi JN, Gupta RK, Al-Muzairi I, Samhan M, Mozavi M, Chugh TD: Invasive fungal infections in renal transplant recipients. J Infect 1996; 33: 95-101
12. Adriaenssens K, Jorens Pg, Meuleman L, Jeuris W, Lambert J: A black necrotic skin lesion in an immuncompromised patient. Diagnosis: Cutaneous mucormycosis. Arch Dermatol 2000; 136: 1165-1170
13. Fisher J, Tuazon CU, Geelhoed GW: Mucormycosis in transplant patients. Am Surg 1980; 46: 315-322
14. Feuilhalde M, Revuz J, Toraine R: Primary cutaneous mucormycosis in a renal transplant patient. Ann Dermatol Venereol 1982; 109: 765-766