

Short communication

Invasive filamentous fungal infections associated with renal transplant tourism

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Abstract: 'Transplant tourism,' the practice of traveling abroad to acquire an organ, has emerged as an issue in kidney transplantation. We treated a patient who developed invasive aspergillosis of the allograft vascular anastomosis after receiving a kidney transplant in Pakistan, prompting us to review the literature of invasive mycoses among commercial organ transplant recipients. We reviewed all published cases of infections in solid organ transplant recipients who bought their organs abroad and analyzed these reports for invasive fungal infections. Including the new case reported here, 19 cases of invasive fungal infections post commercial kidney transplant occurring in 17 patients were analyzed. Infecting organisms were *Aspergillus* species (12/19; 63%), *Zygomycetes* (5/19; 26%), and other fungi (2/19; 5%). Invasive mold infections were present at the transplanted graft in 6/17 patients (35%) with graft loss or death in 13/17 (76%) of patients and overall mortality (10/17) 59%. Invasive fungal infections, frequently originating at the graft site, have emerged as a devastating complication of commercial renal transplant and are associated with high rates of graft loss and death.

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Key words: commercial; transplant; fungal; kidney transplant; transplant tourism; invasive fungal infections; mucormycosis; aspergillosis

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Received 28 May 2009, revised 13 August, 24 September 2009, accepted for publication 12 October 2009

DOI: 10.1111/j.1399-3062.2010.00498.x

Transpl Infect Dis 2010

As the prevalence of end-stage kidney disease (ESRD) continues to increase worldwide, the demand for kidney transplants and hence the size of the waiting list also disproportionately increases. The time waiting for a transplant may be several years, fostering 'transplant tourism,' the practice of traveling abroad to acquire a kidney transplant. Fueled by problems of organ availability, long waiting times, and high medical and surgical costs, patients are increasingly traveling to developing countries to receive kidneys from paid living donors (1). It is estimated that commercial transplantation accounts for 5–10% of the kidney transplants performed annually throughout the world (2). This practice is fraught with ethical and medical complexities including high rates of infectious and other complications (3–6). One potentially devastating complication is developing invasive filamentous fungal infection. Such infections are difficult to diagnose and treat and are frequently associated with high rates of graft loss and death. We recently saw a patient who developed invasive aspergillosis of the renal allograft and vascular anastomosis following travel to South Asia for kidney transplantation.

This case prompted us to review the literature of invasive mycoses among commercial kidney transplant recipients.

Methods

We performed a Medline (National Library of Medicine, Bethesda, Maryland, USA) search from 1966 to 2009 with the terms 'transplant' and 'commercial,' 'living unrelated,' and 'tourism.' The abstracts of retrieved articles were reviewed and those that focused on infections of commercial transplantation were obtained in full, and their reference lists were searched for further articles.

Only English-language articles were included. Cases of invasive fungal infections in patients who traveled abroad for kidney transplantation were analyzed further for site of infection, infecting organisms, and outcomes. Additionally, a previously unreported case seen at our institution is reported herein.

Case report

At presentation to our hospital, the patient was a 66-year-old man with ESRD due to immunoglobulin-A nephropathy who underwent a commercial, living unrelated, kidney transplant in Pakistan in July 2006. In December 2006, a right mid-external iliac artery aneurysm was discovered 6–7 mm distal to the transplant artery and repaired with an endograft. The aneurysm was thought to be due to arterial injury at the time of the transplant. Because the aneurysm was repaired via a percutaneous endovascular procedure, pathology specimen was not obtained. One month later, in January 2007, he fell, sustaining a right knee injury without obvious breaks in the skin, and underwent arthroscopic meniscus repair and intraarticular corticosteroid injection. Several weeks later, he underwent arthrocentesis for ongoing right knee pain and swelling, and synovial cultures showed that the knee was infected with *Aspergillus flavus*. Chest radiograph at that time was remarkable for interstitial pulmonary infiltrates. Stains and cultures of bronchoalveolar lavage fluid and lung biopsy material were negative for fungus. Magnetic resonance imaging of the brain did not show signs of infection.

The patient was treated with a right knee arthrotomy and synovectomy. Voriconazole was initiated intravenously at 6 mg/kg \times 2 doses followed by 4 mg/kg twice daily, and then at 600 mg daily by mouth. Over the next few months, his renal function declined. Two months after initiation of antifungal therapy, a sonogram revealed a 3.5 \times 4 cm aneurysm proximal to the endograft in the right external iliac artery with involvement of the renal transplant arterial anastomosis. During repair of the aneurysm, 10–15 mL of purulent material was removed, the aneurysm was repaired, and the renal allograft was explanted. Gomori's methenamine silver stain of aneurysm tissue showed fungal hyphal elements within the lumen and sub-luminal aspect of the vascular wall consistent with aspergillosis, but the organism failed to grow on fungal culture. The patient was treated with a prolonged course of voriconazole and is doing well on hemodialysis at >1 year after surgery with no evidence of recurring infection.

Results

Including the new case reported here, we identified 19 cases of invasive mold infections in 17 patients who had traveled abroad for renal transplantation. Distribution of organisms, location of transplantation and subsequent care, sites of infections, and outcomes are shown in Table 1 (7–13). Infecting organisms were *Aspergillus* species (12/19; 63%),

Zygomycetes (5/19; 26%), *Ramichloridium mackenziei* (1/19; 5%), and *Pseudallescheria boydii* (1/19; 5%).

Infections were reported as disseminated or extrapulmonary in 100% of cases. Allograft infection was reported in 6/17 (35%) patients, and central nervous system involvement in 5/17 (29%) patients. Graft loss was reported in 13/17 (76%) patients, and overall mortality was 10/17 (59%). The transplant recipients were most commonly from Turkey and the Middle East (8/17; 47%), and North America (6/17; 35%). All transplants were performed in Asia or the Middle East.

Discussion

The advent of transplant tourism adds layers of psychosocial, economic, and medical complexities to the practice of solid organ transplantation. Infections have emerged as a major complication in this group (4, 10, 14). Herein, we report on 19 cases of invasive mold infections in 17 patients who traveled to Asia or the Middle East for kidney transplants. The most common infections were invasive aspergillosis and mucormycosis. All infections were either reported as disseminated or extrapulmonary, and direct fungal involvement of the allograft was seen in 35% of cases. Outcomes of infection were devastating. Overall mortality was 59%, and 82% of the patients sustained allograft loss, major neurological injury, or death.

Rejection and infection are major problems in commercial organ transplant recipients (5, 9, 10). Management of patients after returning to their country of origin is complicated by incomplete information regarding the donor selection, including screening for infectious diseases, and recipient management in the perioperative period. Use of immunosuppressive agents frequently is suboptimal, which may be associated with early allograft rejection (5, 9). Recipients of commercial transplants may be at particular risk for invasive fungal infections because postoperative complications, repeated bacterial infections, and renal insufficiency are all risk factors (15). Developing an invasive fungal infection carries particularly high rates of graft loss and death (16), as noted in this series. These factors also likely cause an increase in the net state of immunosuppression in this population and thereby contribute to the high rates of disseminated fungal infections. Physicians caring for patients involved in transplant tourism should maintain a high level of vigilance for such opportunistic infections. Creation of a North American registry of transplant tourism-associated complications will likely shed further light on the epidemiology of infections in this population.

Invasive fungal infections post commercial kidney transplant: 19 cases occurring in 17 patients

Patient no.	Infecting organism	Residence	Region of transplant	Site of infection	Allograft infection	Graft loss	Outcome	Reference
1	<i>Aspergillus flavus</i>	USA	Pakistan	Knee, renal artery	Yes	Yes	Alive ¹	Present report
2	<i>Aspergillus fumigatus</i>	Saudi Arabia	Philippines	Spine	No	Not reported	Died	(7)
3	<i>Aspergillus</i> species	Turkey	Asia or Middle East	Disseminated	No	Not reported	Died	(8)
4	<i>Aspergillus</i> species	USA	Asia	Brain	No	No	Died	(9)
5	<i>Aspergillus</i> species	Canada	Asia or Middle East	Disseminated	Not reported	Not reported	Died	(10)
6	<i>Aspergillus</i> species	Canada	Asia or Middle East	Disseminated	Not reported	Not reported	Died	(10)
7	<i>Aspergillus</i> species	Canada	Asia or Middle East	Disseminated	Not reported	Not reported	Not reported	(10)
8	<i>Aspergillus</i> species	Canada	Asia or Middle East	Disseminated	Not reported	Not reported	Alive	(10)
9	<i>Aspergillus</i> species	Australia	Lebanon	Kidney	Yes	Yes	Alive	(11)
10	<i>Aspergillus</i> species	Turkey	Asia or Middle East	Brain	No	Not reported	Died	(8)
11	<i>Aspergillus</i> species	Turkey	Asia or Middle East	Urinary tract	Yes	Not reported	Alive	(8)
12	<i>Aspergillus terreus</i>	Slovenia	India	Wound	No	Yes	Died	(12)
7	<i>Pseudallescheria boydii</i>	Canada	Asia or Middle East	Brain abscess	No	Not reported	Not reported	(10)
13	<i>Ramichloridium mackenziei</i>	Saudi Arabia	Iran	Brain abscess	No	No	Alive ¹	(7)
14	<i>Zygomycetes</i>	Belgium	India	Kidney	Yes	Yes	Alive	(13)
12	<i>Zygomycetes</i>	Slovenia	India	Kidney	Yes	Yes	Died	(12)
15	<i>Zygomycetes</i>	Turkey	Asia or Middle East	Rhino-cerebral	No	Not reported	Died	(8)
16	<i>Zygomycetes</i>	Turkey	Asia or Middle East	Kidney	Yes	Yes	Died	(8)
17	<i>Zygomycetes</i>	Saudi Arabia	Pakistan	Liver	No	Yes	Died	(7)

¹Sustained severe neurological injury.

Table 1

In this series, extrapulmonary involvement was seen in all 12 patients with invasive aspergillosis. Infection in 3 patients involved the transplanted kidney, adjacent vasculature, or urinary tract without concomitant lung infection. Three of the 4 patients with mucormycosis had renal allograft involvement. These rates are unusually high. Whereas spread of *Aspergillus* to the kidney may occur in 50% of cases of disseminated aspergillosis, isolated renal involvement is very uncommon (17, 18). Likewise, renal mucormycosis is an uncommon complication of kidney transplantation. In one series of 106 solid organ transplant recipients with mucormycosis, 6 (5.2%) had infections involving the renal allograft (19). Although filamentous fungal infections are generally acquired by inhalation, direct inoculation of tissues may also occur with exposure to a contaminated source. The high rate of allograft infection suggests either infected donors or breaches in asepsis during organ procurement, transport, and/or implantation. Potential sources include fungal contamination of the media used to preserve/transport the donor kidney, or inoculation of the surgical site by airborne fungal spores. Alternatively, the primary source of infection may be due

to fungal inoculation at a site distant from the allograft with secondary dissemination to the kidney.

In conclusion, the practice of commercial transplantation is fraught with complex psychosocial, economic, ethical, and medical issues. In this paper, we describe the emergence of invasive fungal infections, frequently originating at the graft site and associated with high rates of graft loss and death, as another devastating complication of commercial renal transplantation, and should give added impetus to either banning or regulating the practice.

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