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ORIGINAL ARTICLE

Fusarium peritonitis concomitant to kidney transplantation successfully managed with voriconazole: case report and review of the literature

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Summary

Fusarium infections in solid organ transplant recipients are often localized, occur later in the post-transplantation period, and have a better outcome than fusarial infections in patients with hematologic malignancies or bone marrow transplants. We report the first case of proven peritonitis caused by *Fusarium* species in a renal transplant recipient which is also the first successfully managed with voriconazole. We also review previously reported cases of fusarial infection in solid organ transplant recipients.

Introduction

The incidence of invasive fungal infections is increasing and they are the main cause of infectious disease-related mortality following transplantation. *Fusarium*, a common soil mold, is one of the emerging fungal pathogens causing infections in this patient group, although reports of fusariosis in solid organ transplant recipients remain rare. Fungal peritonitis caused by *Fusarium* is an equally uncommon event and has been reported mostly in immunosuppressed individuals with severe underlying disease. We describe not only the first case of a renal transplant recipient with *Fusarium* peritonitis, but also the first successfully managed with voriconazole, and we review the published experience with this infection among solid organ transplant recipients.

Case report

A 56-year-old white woman presented with a medical history of type 2 diabetes since 1990, complicated by diabetic retinopathy and nephropathy, arterial hypertension, hypercholesterolemia, and ischemic cardiopathy. Due to the progression of renal failure, the patient underwent peritoneal dialysis. At 29 months, the peritoneal dialysis fluid became turbid without clinical symptoms. An empirical antimicrobial therapy (day 1) was started with vancomycin (1 g i.v., one dose), gentamicin (2 g i.v./day) and ceftriaxone (2 g i.v./day).

Laboratory examination of a peritoneal fluid swab revealed the following total cell count: 155; macrophages, 27%; lymphocytes, 9%; neutrophils, 59%; eosinophils, 2%; mesothelial cells, 1%; plasmocytes, 1% and basophiles, 1%. The hemogram performed at the same time yielded the following results: hemoglobin, 88 g/l; hematocrit, 27%; WBC, 9.1 g/l; segmented neutrophils, 85%; nonsegmented neutrophils, 8%; eosinophils, 1%; basophils, 0%; monocytes, 5%; lymphocytes, 1%; and platelets, 166 g/l. Renal impairment at that time manifested as 862 μmol/l plasma creatinine and 21.6 mmol/l BUN. Other laboratory values were in the normal range. A compatible cadaver kidney donor became available the

following day, and a renal transplant (day 3) was performed 2 days after initiation of the antimicrobial therapy. The continuous ambulatory peritoneal dialysis catheter was removed. The initial immunosuppressive therapy consisted of anti-human T lymphocyte immunoglobulin (ATG), mycophenol mofetil and prednisone.

The peritoneal fluid cultured on day 1 did not grow any bacteria, but the antimicrobial therapy was continued. On day 5, the initial peritoneal fluid yielded *Fusarium* sp. resistant to amphotericin B, fluconazole and itraconazole, but susceptible to voriconazole. Voriconazole treatment was therefore initiated with a loading dose of 6 mg/kg/12 h the first day followed by a maintenance dose of 4 mg/kg/i.v./12 h. On day 6, increased liver enzymes (ASAT 44 U/l, ALAT 148 U/l) were noted. Voriconazole may have been responsible for the altered liver tests, although it was administered only for a short period. Pretransplantation serologies were positive for cytomegalovirus (CMV) (IgG negative, IgM positive) and compatible with a posthepatitis B virus vaccine. The concomitant immunosuppressive treatment with ATG raised the suspicion of a possible CMV reactivation possibly responsible for the altered liver tests. The CMV viremia (104 copies/ml) diagnosed by an ultrasensitive PCR supported this hypothesis, and valganciclovir (900 mg/p.o./12 h) was started. One week after treatment, CMV viremia was undetectable, and liver tests returned to normal values. This suggests that voriconazole was not responsible for the alteration of the liver tests. After 2 months of voriconazole treatment, the peritoneal infection was considered cured. No adverse events were noticed during the treatment period. The patient remained free of recurrent infection and no other opportunistic infections occurred during a follow-up of 6 months (June 2004). The renal function stabilized with a creatinine plasma level of 155 μmol/l (35–88 μmol/l), and the immunosuppressive regimen consisted of cyclosporine, mycophenol mofetil and prednisone.

Discussion

Invasive fungal infections represent a major complication of organ transplantation. Over the past 20 years, the incidence of fungal infections in transplant recipients has increased, and now affects as many as 50% of bone marrow transplant recipients with neutropenia and 5–20% of solid organ transplant recipients [1,2]. Because of improvement in diagnosis and treatment of CMV infections, invasive fungal infections have now become the leading cause of infection-related mortality following transplantation.

The widespread prophylactic use of fluconazole has led to a decline of *Candida* infections [3,4]. However, the subsequent changes in *Candida* epidemiology have resulted in the emergence of other less susceptible fungal pathogens complicating both bone marrow and solid organ transplantation [5–9]. In addition to aspergillosis, infections caused by other molds that exhibit resistance to conventional antifungal agents have increased in solid organ transplant recipients. Patients with non-*Aspergillus* molds were more likely to have prior CMV infection (30% of such infections), suggesting profound immunosuppression [9]. The use of highly immunosuppressive regimens to prevent rejection favors the emergence of these infections [10,11]. While the incidence of fusariosis in solid organ transplant recipients is rare (lower than that of zygomycosis (<1–9%) [12]), it is more frequent in neutropenic cancer patients [13].

Fusarium spp. are emerging as pathogens that can cause serious opportunistic infections in patients with bone marrow suppression and neutropenia [14–16]. They have also been reported to cause 15% of invasive fungal infections occurring in patients with hematologic malignancies [17]. In contrast, *Fusarium* species have rarely been reported to cause infections among solid organ transplant recipients [12].

Fusarium species are plant pathogens and soil saprophytes that cause a broad spectrum of human infections [18]. They cause mycotoxicosis following ingestion of fusarial toxins or tissue invasion. Localized infections occur in both immunocompromised and immunocompetent hosts. Disseminated fusarial infections occur mostly in patients with hematologic malignancies with myelosuppressive chemotherapy or in patients with severe immune deficiency. The most frequent species causing infections in humans are *Fusarium solani*, *F. oxysporum* and *F. moniliforme* [18]. Fusariosis has widely been reported in hematopoietic stem cell transplant recipients with different clinical presentations, such as disseminated fusariosis with positive blood cultures (48%) and disseminated skin lesions [19–22]. Cases of *Fusarium* peritonitis reported in the literature to date have been always related to patients under peritoneal dialysis without organ transplantation [23–31]. Fusarial infections that occur after solid organ transplantation tend to be localized, and the outcome of such infections is better than that of patients with neutropenia, who more often present disseminated infections.

Series of *Fusarium* infections following solid organ transplantation are rarely reported in the literature. We conducted a review of cases reported in the literature, including the case described here, and summarize these in Table 1.

The patient described in the present report was transplanted during an acute peritoneal infection while microbiological cultures were pending. Even with the suspicion

Table 1. Description of reports in the English-language literature on fusarial infection in solid organ transplant recipients.

References	Organ transplantation	Age (median 42 years)	Gender	Immunosuppressive therapy	Site of infection	Time of onset (median 23.5 months)	Treatment	Outcome of infection
Young & Meyers [45]	Kidney	30 years	F	Unknown	Localized, cutaneous	5 years after transplantation	Surgical excision	Resolved
Heinz *et al.* [46]	Kidney	48 years	M	Cyclosporine, prednisone	Localized, cutaneous (heel)	21 weeks after transplantation	Surgical amputation	Resolved
Arney *et al.* [59]	Lung	53 years	M	Cyclosporine, azathriopin, prednisone	Lung abscesses	12 weeks after transplantation	Abelcet 12.6 g	Resolved
Guinvarc'h *et al.* [22]	Lung	18 years	F	Cyclosporine, azathriopin, prednisone	Disseminated, endocarditis	2 weeks after transplantation	Amphotericin B	Resolved
Sampathkumar & Paya [47]	Heart, Lung	45 years	M	Cyclosporine, azathriopin, prednisone	Localized, cutaneous	1 year after transplantation	Abelcet 10 g; and topical fungizone	Resolved
Girardi *et al.* [48]	Kidney	50 years	M	Cyclosporine, azathriopin	Localized, cutaneous (foot)	2 years after transplantation	Surgical debridement, AmBisome 7.5 g	Not resolved
Cocuroccia *et al.* [20]	Kidney	53 years	M	Cyclosporine, prednisone	Localized, cutaneous (leg)	4 years after transplantation	Itraconazole 200 mg/day for 6 weeks	Resolved
2004 (present report)	Kidney	56 years	F	ATG, mycophenol mofetil, prednisone	Peritoneal	During transplantation	Voriconazole 8 mg/kg/day for 2 months	Resolved

of a peritoneal infection, which did not correspond to the ideal conditions to carry out solid organ transplantation, a renal transplantation was performed. This decision was made because the patient had been waiting for a compatible donor for 2 years.

Fusarium infections characteristics

Localized superficial and deep-seated fusariosis have been described in both healthy and immunocompromised hosts. Patients with cutaneous lesions can present with superficial and deep infections as well as toxic reactions. Skin and soft tissue involvement associated with *Fusarium* infection can result either from direct invasion of skin structures, or as a manifestation of disseminated infection.

Fusarium skin infection can present as erythematous papules and nodules with necrosis and subcutaneous nodular lesions, as onychomycosis, intertrigo, finger cellulitis, pustules, ecthyma gangrenosum-like lesions and mycetoma [32–36]. Although facial granuloma is ordinarily an indolent condition, it can rapidly lead to disseminated infection in immunocompromised patients. *Fusarium* spp. may also colonize wounds, burns, and ulcers.

Biopsy and culture of skin lesions can help establish an early diagnosis of *Fusarium* infection. Like *Aspergillus* spp., *Fusarium* spp. may invade blood vessels and result in tissue necrosis and pulmonary cavitations. In the immunocompromised patient, a superficial, localized infection may disseminate through lymph and/or blood [37,38]. Disseminated fusariosis can affect almost any organ and is defined as involvement of two noncontiguous sites in association with more than one positive blood culture [14,37]. It is usually reported in neutropenic patients with hematologic malignancy, especially acute leukemia, bone marrow transplant recipients, and, more rarely, patients with solid tumors [14,38]. The skin is often the initial clue to diagnosis as cutaneous lesions are observed in about 85% of patients with disseminated *Fusarium* infection and often occur at an early stage of the disease [14,32,37]. Diagnosis is based on mycology and histopathology. *Fusarium* species can be isolated from cultures of blood samples in 50–70% of cases [14]. PCR techniques are used for the detection of *Fusarium* species in blood and clinical samples [39,40].

The outcome of infection because of non-*Aspergillus* molds (*Fusarium*, *Scedosporium*, and Zygomycetes) in hematopoietic stem cell transplant recipients is usually poor, as the patient's immune system is depressed [41] and there is low sensitivity of the pathogens to antifungal therapy [42,43].

Disseminated *Fusarium* infection carries a poor prognosis, which is related to the angiotropism of *Fusarium*

and its capacity for adventitious sporulation in tissues [44], as well as the underlying disease, the presence of neutropenia (<500 cells/μl), and late diagnosis and treatment. Only those patients in whom neutropenia has resolved do recover [15,19].

While the majority of solid organ transplant recipients with *Fusarium* infection survive [20,22,45–49], the mortality rate in patients with hematopoietic stem cell transplantation is very high (70–90%) [14,39,49,50]. *Fusarium* infections in solid organ transplant recipients are less common and mostly localized, and the onset of infection occurs later in contrast to hematopoietic stem cell transplant recipients. *Fusarium* peritonitis can complicate the condition of patients who undergo chronic peritoneal dialysis.

Treatment

Fusarium species are relatively resistant to treatment with antifungal agents. *In vitro*, amphotericin B is the most effective of the antifungal agents. Fluconazole, itraconazole, and flucytosine have no activity against *Fusarium* species, and ketoconazole, miconazole, and terbinafine have limited activity [51–53]. Amphotericin B is the drug of choice but high doses are needed, and side effects may increase. The liposomal formulations are less toxic but are costly. Topical treatment, such as amphotericin cream 3%, can be paired with systemic antifungal treatment in cases of superficial cutaneous infections or corneal ulcers [54]. Topical nystatin is effective in treating *Fusarium* infections in burn patients [55].

Surgical treatment also plays an important role in managing localized infection. Localized surgical resection or amputation of a limb has resulted in the cure of fusarial soft tissue infections in transplant recipients [46,47].

The new triazole agents (voriconazole, posaconazole, and ravuconazole) exhibit activity against these fungi [56] and are used for the treatment of fusariosis. Voriconazole was reported as a successful treatment of disseminated fusariosis in patients with hemato-oncologic malignancies [57] or refractory fungal infections [58]. In contrast to other solid organ transplant recipients reported with *Fusarium* infections, the patient reported in the present study was transplanted during an active infection and treated for 8 weeks with voriconazole with an excellent outcome and without adverse events.

Conclusion

The clinical spectrum of invasive fungal infections in transplant recipients has changed over the past decade, with a reduction in candidiasis and an increase in mold infections. Although *Aspergillus* spp. are by far the most frequent mold infections in transplant recipients, reports of infections caused by other molds have increased. *Fusarium*, *Scedosporium*, and Zygomycetes are examples of these pathogens. These infections tend to be disseminated, and prognosis is poor because these fungi are resistant to most available antifungal agents. New drugs, particularly the new triazoles, may have a role in the treatment and prophylaxis of these infections, but available data remain scant. In addition to antifungal treatment, strategies to improve the host defences and surgical intervention to remove necrotic tissue are important measures that may improve the prognosis for these infections.

In some cases, the ideal conditions to perform a solid organ transplantation are not met. In the present case, the patient was operated with the suspicion of a peritoneal infection which was confirmed later; the reason was that the patient had been on the waiting list for 2 years. But fortunately, with the use of the new triazole, voriconazole, the infectious episode was cured, and no re-infection occurred.

Voriconazole becomes a very important tool in the treatment of this type of infections because of the safety and efficacy of the drug.

Conflict of interest

No funding sources support this work.

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