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Minireview

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Mucormycosis (zygomycosis) of renal allograft

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Abstract
Fungal infection is relatively common among renal transplant recipients from developing countries. Mucormycosis, also known as zygomycosis, is one of the most serious fungal infections in these patients. The most common of presentation is rhino-cerebral. Isolated involvement of a renal allograft is very rare. A thorough search of literature and our medical records yielded a total of 24 cases with mucormycosis of the transplanted kidney. There was an association with cytomegalovirus (CMV) infection and anti-rejection treatment in these patients and most of these transplants were performed in the developing countries from unrelated donors. The outcome was very poor with an early mortality in 13 (54.5%) patients. Renal allograft mucormycosis is a relatively rare and potentially fatal complication following renal transplantation. Early diagnosis, graft nephrectomy and appropriate antifungal therapy may result in an improved prognosis for these patients.

Keywords: cytomegalovirus infection; immunosuppression; mucormycosis; renal allograft

Background

Renal transplant recipients are prone to developing opportunistic infections due to their immunosuppressed state [1–3]. Among these, the Zygomycetes class of filamentous fungi causes the most devastating disease following renal transplantation [1, 2]. The pathogenic fungi of this class belong to the order Mucorales, and the family Mucoraceae [4]. Those commonly reported in renal transplant recipients have included the genera (species) of Rhizopus (oryzae), Mucor (circinelloides) and Absidia (corymbifera) now called Lichteimia [5]. Mucormycosis, now a preferred term over Zygomycosis on the basis of taxonomy [4], commonly presents as rhino-sino-orbital infection. It also causes rhino-cerebral, pulmonary, disseminated, gastrointestinal, cutaneous and genitourinary infections [6]. Involvement of a renal allograft in the isolated or disseminated form is rare, and have generally been published as individual case reports, most commonly living unrelated kidney donor transplantations with poor outcomes [7–25]. This review focuses on 24 cases of renal allograft mucormycoses, highlighting their clinico-pathological features with analysis of risk factors and management of this serious condition.

Literature review

We identified 22 cases of renal allograft mucormycosis in transplant patients listed in Medline (PubMed, Ovid, Scopus) and Embase. In addition, we included two patients with renal allograft mucormycosis seen at our center. The inclusion criteria comprised of evidence of positive staining with periodic acid-Schiff and Gomori's methenamine silver stains, suggestive of mucormycosis, in the histology sections of renal allograft (obtained at renal biopsy or at autopsy). The pathogenic fungi were identified by their broad aseptate hyphae having right-angled branching typical of the Zygomycetes family [4]. The clinico-pathological features of the cases are described in Table 1.

Results

There were 16 males and 8 females. The mean (SD) age at the time of diagnosis was 43 ± 16 years. The diagnosis of mucormycosis was made after 73 ± 119 days (range 7 days to 18 months) of renal transplantation. Only 9 patients received a kidney from related donors; the remaining 15 received the transplanted kidney from unrelated donors, including 5 from deceased donors, (2 from the same donor; cases 13 and 14). Live unrelated renal transplantation in 10 patients was done in India [17], Egypt [2] and Pakistan [3]. All patients had received routine immunosuppression in the post-transplant period including prednisolone, cyclosporine, tacrolimus, azathioprine or mycophenolate in varying combinations as shown in Table 1.

The primary kidney disease resulting in end-stage kidney failure was chronic glomerulonephritis in 13 patients, diabetes mellitus in 4, polycystic kidney disease

Table 1. Clinico-pathological features of renal allograft mucormycosis[a]

S No. [ref no]	Age/ sex	Aetiology/ comorbidity	Donor	Post Tx Dx -days	Clinico-laboratory manifestations	Immunosuppression induction/ART	Imaging USG/CT/ Doppler	Histo- Bx/Nx culture	Treatment details	Outcome
1 [17]	59/F	CGN	LURT-(India)	1 month	Fever, RF, graft tend CMV + Candidial UTI	Pred/CSA/AZA ART + (Bx ACR+)	NA	Graft biopsy	Graft Nx + Ampho-B × 4 days	Died
2 [7]	49 M	CGN	LRRT	18 months	Fever, RF, graft tend CMV+	Pred/CSA ART + (Bx ACR +), ATG+	Enlarged graft	Nx. Specimen *Mucor*	Graft Nx + BSA Ampho-B −ve	Died
3 [11]	42/M	CGN	LURT-(Egypt)	45 days	Fever, RF, graft tend	Pred/CSA/AZAART+	Enlarged graft CT/PG collection ↑ resistive index	Graft biopsy *Mucor*	Graft Nx + Ampho-B × 5 days	Died
4 [22]	14/M	B/L PUJ/Obstr uro	LRRT	3 months	RF, graft tend	Pred/CSA/AZA ARTX2 (Bx ACR+) OKT3 + ATG,	Enlarged graft (CT)	Nx. specimen *Mucor*	Graft Nx + Ampho-B × 5 days	Died
5 [9]	42/M	CGN	LURT-(Egypt)	35 days	RF fever ↑ TLC CMV PCR+	Pred/CSA/MMF ART + (Bx ACR+)	Enlarged graft CT/PG collection ↑ resistive index	Nx. specimen Disseminated	Graft Nx + Ampho-B × 4 days	Died
6 [9]	52/F	DM	LURT-(Egypt)	25 days	Fever, RF, graft tend CMV PCR+	Pred/CSA/MMF	Enlarged graft with air (CT) PG collection	Nx. specimen	Graft Nx + Ampho-B × 3 weeks TD 2.5 g	Survived
7 [15]	18/F	ADPKD, HCV	LURT-(India)	25 days	Fever, RF, graft tend HCV	Pred/CSA/AZA ART (ACR+)	Enlarged graft	Graft biopsy	Graft Nx + Ampho-B × 3 weeks TD 2.5 g	Survived
8 [14]	52/M	CGN	LRRT	8 days	Graft tend	Pred/CSA/AZA induction-baxiliximab	Peri-grafthematoma	Nx. specimen	Diagnosis PM	Died
9 [23]	51/M	HSP-nephritis ESRD	LURT-(India)	2 months	Fever, RF, graft tend disseminated-CMV + (allograft) *Escherichia Coli* UTI	Pred/CSA/AZAART+	NA	Graft biopsy *Absidia corymbifera*	Graft Nx + alone	Survived
10 [18]	30/F	CGN	LRRT	10 days	Fever, RF, graft tend	Pred/CSA/AZA ART+	CT-PG collection	Graft biopsy	Graft Nx + Ambisome × 4 days	Died
11 [21]	53 M	CGN	LURT-(India)	2 months	Odynophagia, RF CMV + (allograft) Aspergillosis lung	Pred/CSA/AZA	Thyroid abscess. Large kidney	Autopsy disseminated	Diagnosis PM	Died
12 [12]	19 F	NA	DDRT	4 months	*Candida P aerogenosa K pneuminie*	Pred /AZA	NA	Nx. specimen	Diagnosis PM	Died
13 [8]	61 M[b]	CGN	DDRT	7 days	Fever, RF	Pred/TAC induction with ATG	CT-multiple air fluid levels	Nx. specimen disseminated *A. elegans*	Graft Nx + ABLC/AMB × 4 d	Died
14 [8]	31 F[b]	CGN	DDRT	12 days	Fever RF, graft tend	Pred/TAC induction with ATG	CT-peri-graft fat stranding	Nx. Specimen *A. elegans*	Graft Nx + ABLC/Amb × 1 m (=40 g)	Survived
15 [24]	31 M	B/L PUJ/Obstr uro	DDRT	2 months	Graft tend Hematuria	Pred/CSA/AZA ART+	US graft swelling	Nx. specimen	Graft Nx + Ampho-B	Survived
16 [24]	58 F	ADKD	LURT-(India)	9 months	Fever RF, graft tend UTI Org	Pred/CSA/AZA ART+	NA	Nx. specimen	Graft Nx + Ampho-B × 5 weeks	Survived
17 [19]	22 F	CGN	LRRT	2 months	Fever RF graft tend UTI *E. coli*	CSA MMF PRED	Enlarged graft ↑ resistive index	Graft biopsy	Graft NX + AMPHO-B × 4 days	Died
18 [20]	52 M	CGN	DDRT	2 months	Fever RF graft tend	Induction- baxiliximab and ART CSA, Pred + OKT3 no response + (ACR 2)	Enlarged graft ↑ resistive index	Nx. specimen	Graft Nx + Ampho-B × 6 weeks dose 2 g	Survived

(*continued*)

Table 1. Continued

S No. [ref no]	Age/ sex	Aetiology/ comorbidity	Donor	Post Tx Dx -days	Clinico-laboratory manifestations	Immunosuppression induction/ART	Imaging USG/CT/ Doppler	Histo- Bx/Nx culture	Treatment details	Outcome
19 [16]	62 M	DM	LURT-Pakistan	3 weeks	Fever, RF	PRED CSA MMF NIGERIAN IN USA Lurt Pakistan	Enlarged graft, Hydronephrosis ureteral stenosis	Graft biopsy Culture Mucor	Graft Nx + Ampho-B + D 6 weeks Posaconazole	Survived
20 [13]	42 M	DM	LRRT	1 month	Fever, graft tend. RF	PRED CSA MMF Absent	USG enlarged Graft	Graft Bx	Graft Nx + Ampho-B × 7 days	Died
21 [25]	59 M	HCC, Liver Tx 10 yrs back	DDRT	6 weeks	Incision site infection. Graft Tend. RF	PRED TAC MMF induction with ATGAM	NA	Graft biopsy	Graft Nx + liposome AmB	Survived
22 [10]	18 M	CGN	LRRT	1 month	Fever, graft tend. RF	PRED TAC MMF	NA	Renal artery thrombosis Nx Specimen	Graft Nx + Ampho-B+	Died
23	46 M	DM	LURT-(India)	2 months	Fever RF graft tend	PRED CSA MMF	Enlarged graft	Graft biopsy	Graft Nx + Ampho-BX4 weeks	Survived
24	59/M	CGN	LURT-(India)	14 days	Fever RF graft tend CMV + UTI (pseudo)	Pred/CSA/AZA	Enlarged graft PG collection Hypodense lesion on CT	Graft biopsy + Nx Specimen	Graft Nx + Ampho-B × 4 weeks	Survived

[a]Pred, prednisolone; AZA, azathioprine; MMF, mycoiphenolate; CSA, cyclosporine; TAC, Tacrolimus. Unpublished cases: LURD, live unrelated renal transplantation; LRRD, live related renal transplantation; NA, information not available; ART, anti-rejection treatment; PG, perigraft; Nx, nephrectomy.
[b]Received kidney from the same donor.

in 2, obstructive uropathy in 2, Henoch–Schönlein purpura in 1, hepatocellular carcinoma with liver transplant in 1 and unknown aetiology in 1. The presenting clinical features included renal dysfunction in 20 (83.3%), tenderness over the transplanted kidney in 19 (79.1%) and fever in 18 (75%). There was concomitant bacterial urinary tract infection in seven (29.4%) patients with co-existing Candida infection in one (case 12). Seven patients had coexistent cytomegalovirus (CMV) infection, two of which included allograft involvement (case 9 and case 11). Other comorbid features included the administration of anti-rejection medication with pulse steroids in 11 patients and additional medication in five cases with antilymphocyte antibodies or IL-2 receptor antagonists at induction or in resistant acute rejection episodes.

Radiology was helpful in 17 patients and ultrasonography (USG) showed enlarged allograft in 14 (82%) with peri-graft collection in 5 patients. Computerized tomography was available only in five patients and it confirmed findings of USG. Histology tissue was obtained by an allograft biopsy in 11, and from graft nephrectomy specimens in 13 patients. Diagnosis of mucormycosis was made post-mortem in three cases. The remaining 21 patients had graft nephrectomy specimens (including those in whom diagnosis was already made after renal allograft biopsy). The disease was isolated to the transplanted kidney in 21 patients and disseminated in the remaining three. Among these three, one patient (case 11) presented with swelling of the thyroid gland and showed evidence of disseminated mucormycosis involving the thyroid gland, transplant kidney, lungs, liver, spleen and small intestine. In addition, he had aspergilloma in the lung and CMV nephritis in the allograft [12]. Another patient (case 13) with disseminated mucormycosis had contracted the infection from an infected donor who was involved in a road-traffic accident with prolonged immersion in shallow water [8]. The other recipient of kidney from the same donor (case 14) also had mucormycosis, but it was limited to the renal allograft. This patient survived on dialysis after she underwent prophylactic graft nephrectomy and received a full course of amphotericin therapy. Antifungal medications were initiated in 18 patients who received varying doses of amphotericin-B therapy. Notably, one of them was administered posaconazole with a successful outcome [16]. Among the 11 patients who survived, 10 had adequate dose of amphotericin B besides graft nephrectomy and one (case 9) survived following the graft nephrectomy alone [23]. Overall, prognosis was poor with mortality in 13 (54.5%) of the patients.

Discussion

The Zygomycetes are opportunistic organisms with ubiquitous distribution in soil, decaying organic matter and air [1]. They have minimal intrinsic pathogenicity but are known to initiate an aggressive and often fatal infection under conditions such as diabetic ketoacidosis, lymphoproliferative disorders, organ transplantation, HIV infection and in patients on desferrioxamine therapy [1, 26, 27]. Isolated mucormycosis as well as disseminated infections have been reported in native kidneys of immunocompromised patients other than transplant recipients [28, 29]. Renal allograft involvement, however, is rare and

only four cases had been described until 2001 [11]. In a later review, Almyroudis *et al*. [30] identified only six cases of isolated renal allograft mucormycosis from among 116 cases of mucormycosis of solid organ transplant recipients reported in the literature. In our study, we have reported 24 cases of renal allograft mucormycosis, the largest reported number so far.

Risk factors

Mucormycosis is most commonly acquired during the nadir of immunosuppression between 1 and 6 months post transplantation [2]. Increased immunosuppression for the treatment of rejection is associated with an enhanced incidence of fungal infection [2, 13]. In laboratory models of mucormycosis, corticosteroids have been shown to predispose to the invasion and reactivation of latent infection [31]. Eighty percent of our patients with graft involvement had presented within 3 months of transplantation and it is interesting to note that 50% of them had received acute rejection treatment with steroids. Administration of anti-rejection therapy on mere suspicion of acute rejection or its over treatment (including polyclonal or monoclonal antibodies) might contribute to the development of serious fungal infections like mucormycosis [2, 13], as seen in case number 4 (treated with two courses of intravenous methyl prednisolone and a course of OKT3 and anti-thymocyte globulin).

As a result of widening disparity between organ demand and supply in the developed countries, 'transplant tourism' in developing countries has become increasingly common and is a well-recognized risk factor for serious opportunistic infections [32]. Majority of our patients had received renal grafts from living unrelated donors (62.5%), similar to the experience of Nampoory *et al.* from Kuwait who found that 78% of fungal infections occurred after living unrelated kidney transplantation [17]. Purchase of organs from donors belonging to poor socioeconomic backgrounds, inadequate preoperative evaluation of donor and suboptimal postoperative care may all contribute to opportunistic infections in recipients and poor outcomes [33]. Commercial transplantation goes on despite strict transplant laws in many countries. A possibility of higher environmental load in our country has been speculated as the possible cause of high incidence of renal mucormycosis [28].

It is well known that CMV infection triggers fungal infections such as aspergillosis or candidiasis in renal transplant recipients. However, an association between CMV infection and mucormycosis infection has rarely been reported. Andrews *et al.* [34] first reported the association of CMV colitis and mucormycosis affecting the bone. Ju *et al.* [35] have reported a case of massive lower gastrointestinal bleed caused by mixed infection of CMV and mucormycosis. The association of CMV infection and graft mucormycosis was seen in 30% of our cases including the allograft involvement as well in two of them (cases 9 and 11). The immunosuppressive effect of severe CMV infection may have primed these patients for zygomycotic infection.

In addition to involvement in disseminated mucormycosis, a renal allograft may sometimes get involved by local spread from incision site infection [25] or an ascending infection [36]. Donor-derived fungal infection, as observed in cases 13 and 14 who received kidneys from the same infected donor [8], has been a very well recognized mode of transmission of mucormycosis [37]. In the absence of these factors, isolated renal involvement may result from a subclinical pulmonary infection with hematogenous dissemination to the kidney in a manner comparable with renal tuberculosis [23].

A characteristic feature of Mucorales is strong tropism for invasion of blood vessels causing vascular thrombosis, multiple infarcts and necrosis in affected organs, the pathologic hallmark of mucormycosis [4]. In the kidneys, they have been reported to cause necrotizing cortical and medullary abscesses and infarction with involvement of glomeruli and invasion of arcuate and intralobular vessels [11, 30]. Renal failure is an important complication of renal mucormycosis due to near total occlusion of the renal arteries and their branches and this was the commonest presentation in our cases.

Diagnosis

A definite diagnosis of mucormycosis can only be established by histological examination of the infected tissue. The Mucorales are identified by their broad aseptate hyphae branching at right angles at irregular intervals as against the dichotomously branching septate aspergillus hyphae [38]. Imaging studies including contrast enhanced computerized tomography may help in the diagnosis of this fungal infection with an enlarged kidney having no or poor contrast excretion and presence of perinephric collection suggesting intra-renal abscesses [28]. The use of real-time, quantitative PCR of the blood, broncho-alveolar lavage or infected tissue has been recently recommended for an early diagnosis of mucormycosis [10, 38].

Treatment and outcome

Compared with other filamentous fungi, there has been no major breakthrough in the management of mucormycosis in the last decade, with the majority of patients who develop the infection still dying within 12 weeks of diagnosis [39]. However, early recognition and treatment of invasive mucormycosis syndromes, as well as individualized approaches to treatment, could improve the odds of survival in renal transplant recipients. A successful therapy of renal mucormycosis comprises (i) tissue debridement, i.e. nephrectomy, (ii) withdrawal of immunosuppression and (iii) administration of antifungal therapy. Only two systemic antifungals are currently available with good activity against Mucorales – amphotericin B (including the lipid formulations) and the triazole posaconazole. Amphotericin-B continues to be the gold standard of antifungal therapy, but the conventional formulation is associated with a high incidence of adverse events and resistance in some cases. Patients with renal mucormycosis may benefit from its lipid formulations in view of renal failure that these patients usually have [40]. In addition, we can give higher dose of amphotericin with lipid formulation for a faster control of disease. Posaconazole, new triazole, with its pharmacokinetic advantages and low side-effect profile, has been increasingly used in mucormycosis both as a 'step-down' therapy following initial amphotericin administration and as a 'salvage' therapy in patients with resistance to amphotericin B [41, 42].

In conclusion, graft mucormycosis is a rare complication of renal transplantation. It occurs predominantly in the setting of living unrelated transplantation performed in developing countries. There is an association

between the occurrence of CMV infection and renal allograft mucormycosis. Clinical presentation may resemble acute rejection. Augmentation of immunosuppression, especially with corticosteroids, may further worsen the progression of this serious fungal infection. Although this is the largest review of renal allograft mucormycosis highlighting the common presenting features and its association with co-morbid factors, it is limited by the fact that it is drawn from previously reported cases from different geographic locations and insufficient information. Hence, it is difficult to formulate uniform guidelines for further directions, but a high index of suspicion and timely therapy may help in saving the patients from this fatal disease.

Conflict of interest statement. None declared.

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