Minireview

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...
| S 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 + Amapho-B × 4 days | Died |
| 2 [7] | 49 M | CGN | LURT-India | 18 months | Fever, RF, graft tend CMV + | Pred/CSA ART + (Bx ACR +), ATG + | Enlarged graft | | Graft Nx + BSA Amapho-B × 4 days | Died |
| 3 [11] | 42/M | CGN | LURT-Egypt | 45 days | Fever, RF, graft tend | Pred/CSA/AZA ART+ | Enlarged graft CT/PG collection ↑ resistive index | | Graft biopsy Mucor | Graft Nx + Amapho-B × 5 days | Died |
| 4 [22] | 14/M | B/L PUJ/Obstr uro | LURT-India | 3 months | RF, graft tend | Pred/CSA/AZA ARTX2 (Bx ACR +), OKT3 + ATG, Pred/CSA/MMF ART + (Bx ACR +) | Enlarged graft (CT) | | Graft biopsy | Graft Nx + Amapho-B × 5 weeks | Died |
| 5 [9] | 42/M | CGN | LURT-Egypt | 35 days | RF fever ↑ TLC CMV PCR+ | Pred/CSA/AZA ART + (Bx ACR +), ATG + | Enlarged graft CT/PG collection ↑ resistive index | | | Graft Nx + Amapho-B × 4 weeks | Died |
| 6 [9] | 52/F | DM | LURT-India | 25 days | Fever, RF, graft tend CMV PCR+ | Pred/CSA/MMF | Enlarged graft with air (CT) PG collection | | Graft biopsy Mucor | Graft Nx + Amapho-B × 3 weeks | Survived |
| 7 [15] | 18/F | ADPKD, HCV | LURT-India | 25 days | Fever, RF, graft tend HCV | Pred/CSA/AZA ART (ACR+) | Enlarged graft | | | Graft Nx + Amapho-B × 3 weeks | Survived |
| 8 [12] | 52/M | CGN | LURT-India | 8 days | Graft tend | Pred/CSA/AZA induction-baxiliximab | Peri-graft hematomata | | | 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/AZA ART+ | CT-PG collection | | Graft biopsy | Absidia corymbifera | Graft Nx + alone | Survived |
| 10 [18] | 30/F | CGN | LURT-India | 10 days | Fever, RF, graft tend | Pred/CSA/AZA ART+ | CT-PG collection | | Graft biopsy | | | Died |
| 11 [21] | 53 M | CGN | LURT-India | 2 months | Odyphonogia, RF CMV + (allograft) Aspergilosis lung | Pred/CSA/AZA | Thyroid abscess. Large kidney | | Autopsy disseminated | | | Died |
| 12 [12] | 19 F | NA | DDRT | 4 months | Candida P aerogenosa K pneumonie | Pred /AZA | NA | | Graft biopsy Mucor | | | Died |
| 13 [8] | 61 M b | CGN | DDRT | 7 days | Fever, RF | Pred/TAC induction with ATG | CT-multiple air fluid levels | | | Graft Nx + ABLC/AMB × 4 d | Died |
| 14 [8] | 31 I b | CGN | DDRT | 12 days | Fever, RF, graft tend | Pred/TAC induction with ATG | CT-peri-graft fat stranding US graft swelling | | Graft biopsy Mucor | Graft Nx + Amapho-B × 1 m (40 g) | Survived |
| 15 [24] | 31 M | B/L PUJ/Obs truro | DDRT | 2 months | Graft tend Hematuria | Pred/CSA/AZA ART+ | U.S graft swelling | | Graft biopsy Mucor | Graft Nx + Amapho-B × 1 m (40 g) | Survived |
| 16 [24] | 58 F | ADKD | LURT-India | 9 months | Fever, RF, graft tend UTI Org | Pred/CSA/AZA ART+ | NA | | Graft biopsy Mucor | Graft Nx + Amapho-B × 5 weeks | Survived |
| 17 [19] | 22 F | CGN | LURT-India | 2 months | Fever RF, graft tend UTI E.coli | CSA MMF PRED | Enlarged graft ↑ resistive index | | Graft biopsy Mucor | 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 | | | Graft Nx + Amapho-B × 6 weeks dose 2 g | Survived |

(continued)
| S No. | Age | 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    | 62  | M                     | DM    | 3 weeks         | Fever, RF                       | PRED CSA MMF NIGERIAN IN USA Lurt Pakistan | Enlarged graft, Hydrenephrosis ureteral stenosis USG enlarged Graft | Graft biopsy Culture Mucor | Graft Nx + Ampho-B × 6 weeks Posaconazole | Survived |
| 20    | 42  | M                     | DM    | 1 month         | Fever, graft tend, RF           | PRED CSA MMF Absent             | Enlarged graft         | Graft Bx          | Graft Nx + Ampho-B × 7 days | Died |
| 21    | 59  | M                     | HCC, Liver Tx | 6 weeks | Incision site infection, Graft tend, RF | PRED TAC MMF induction with ATGAM | NA                  | Enlarged graft PG | Graft biopsy | Survived |
| 22    | 18  | M                     | CGN   | 1 month         | Fever, graft tend, RF           | PRED TAC MMF                   | Enlarged graft         | Graft biopsy       | Graft Nx + Ampho-B | Died |
| 23    | 46  | M                     | LURT-(India) | 2 months | Fever RF graft tend | PRED CSA MMF | Enlarged graft PG | Graft biopsy + Nx Specimen | Graft Nx + Ampho-B × 4 weeks | Survived |
| 24    | 59/M | M                     | CGN   | 14 days         | Fever RF graft tend CMV + UTI (pseudo) | Pred/CSA/AZA | Enlarged graft PG | Graft biopsy + Nx Specimen | Graft Nx + Ampho-B × 4 weeks | Survived |

aPred, 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.
bReceived kidney from the same donor.

Discussion

The Zygomycetes are opportunistic organisms with ubiquitous distribution in soil, decaying organic matter, and in patients on desferrioxamine therapy [1, 2]. They have minimal intrinsic pathogenicity but can cause disseminated infection [3]. Isolated mucormycosis has been reported in native kidneys of immunocompromised patients other than transplant recipients [4, 5]. Renal allograft involvement is rare; however, it is known to initiate an aggressive and often fatal infection [6]. Antifungal medications were initiated in 18 patients who received varying doses of amphotericin therapy. Antifungal medications were initiated in 18 patients who received varying doses of amphotericin-B therapy. Among the 11 patients who received antilymphocyte antibodies or IL-2 receptor antagonists at induction or in resistant acute rejection episodes, isolated mucormycosis developed in 10 patients. Diagnosis was established by either transplanted kidney biopsy (19/27) or perigraft collection in 5 patients. Computerized tomography (CT) findings of USG and culture were obtained in 19 patients. Diagnosis was made in 13 patients. Diagnosis of mucormycosis was made post-mortem in three cases. Diagnosis was post-mortem in 13 (58.5%) of the patients. Overall, prognosis was poor with mortality in 12 of 13 patients (92.3%). Renal allograft involvement, however, is rare and tends to present in a more aggressive manner [7].

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In conclusion, isolated mucormycosis should be considered in the differential diagnosis of transplant recipients presenting with fever, graft tenderness, and other clinical features. Early diagnosis and prompt initiation of antifungal therapy are crucial for survival. Renal allograft involvement, however, is rare and tends to present in a more aggressive manner. It is often associated with other infections, including CMV and fungal infections [8]. Among the 11 patients who received antilymphocyte antibodies or IL-2 receptor antagonists at induction or in resistant acute rejection episodes, isolated mucormycosis developed in 10 patients. Diagnosis was established by either transplanted kidney biopsy (19/27) or perigraft collection in 5 patients. Computerized tomography (CT) findings of USG and culture were obtained in 19 patients. Diagnosis was made in 13 patients. Diagnosis of mucormycosis was made post-mortem in three cases. Diagnosis was post-mortem in 13 (58.5%) of the patients. Overall, prognosis was poor with mortality in 12 of 13 patients (92.3%). Renal allograft involvement, however, is rare and tends to present in a more aggressive manner.
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-aveolar 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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