Management of early graft candidiasis in a kidney transplant recipient

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SUMMARY
Balancing adequate immunosuppression with the risk of infection after renal transplantation remains a challenge. The presence of comorbidities adds to the challenge. Although infrequent, invasive fungal infections result in high morbidity and mortality risk in renal transplant recipients. This can be attributed to the intense immunosuppression in the first 6 months after renal transplantation, minimal symptomatology and the high mortality associated with fungal infections. Due to minimal available evidence, clinical judgement guides management of graft candidiasis. There is a need to develop evidence-based management guidelines for the treatment of fungal infections in renal transplants. Here, we report a case of early-onset candidiasis in a transplanted kidney and present the histological findings, multidisciplinary discussions and treatment given.

BACKGROUND
Kidney transplantation remains the treatment of choice for patients with end-stage kidney disease (ESKD).1 It provides a better quality of life and superior outcomes when compared with chronic dialysis therapy.2,3 However, post-transplant survival is hampered by the common causes of post-transplantation mortality such as cardiovascular disease, malignancy and infections.4–7

The risk of infection in transplant recipients is determined by immunosuppression status, individual comorbidities, direct exposure to pathogens or donor-recipient infection transmission.8 It is estimated that 1.3% of renal transplant recipients will develop an invasive fungal infection (IFI).9 Candida species account for the majority (49%) of cases in this population, with Candida albicans being the most responsible organism, followed by Candida glabrata and Candida parapsilosis.9 10 However, there has been a recent observed trend towards non-albicans species associated with IFI, leading to poor outcomes.11 12 The change in epidemiological trends poses an additional increased challenge to the management of IFI, as certain Candida species such as C. glabrata have reduced susceptibility to commonly used antifungals.13 14

Current guidelines recommend early initiation of echinocandins treatment for candidaemia in transplant recipients and consider de-escalation to oral antifungals according to the isolated organism’s response to treatment.15 16 Recommendations to guide optimal antifungal therapy specific to the organism, escalation of medical therapy, and timely consideration of surgical graft nephrectomy are not available due to the dearth of relevant studies in the literature.

We present a case of a renal transplant recipient that developed graft candidiasis in the early days post-transplant.

CASE PRESENTATION
A woman in her 60s with a history of ESKD secondary to interstitial nephritis and insulin-treated type 2 diabetes mellitus received her first cadaveric renal transplant from a donor after brain death. She presented pretransplant with suboptimal glycaemic control (HaemoglobinA1c 84), a body mass index (BMI) of 37.7 kg/m2 and comorbidities that included hypertension and recurrent vaginal candidiasis.

Total ischaemia time was 23 hours and 49 min with a donor/recipient HLA mismatch of 1:1:0. Induction immunotherapy was with basiliximab and intravenous methylprednisolone. We subsequently followed our centre’s immunosuppression maintenance protocol of tacrolimus and mycophenolate mofetil with rapid steroid withdrawal.

The patient remained haemodynamically stable and was catheterised to monitor her urine output. Her parameters and biochemistry throughout the admission are listed in table 1. The kidney perfusion fluid was sterile and showed no growth. Donor urine grew C. glabrata after prolonged incubation. She developed delayed graft function (DGF) but required one haemodialysis session. Nuclear medicine imaging and Doppler ultrasound assessment of the transplanted kidney demonstrated adequate perfusion, non-specific hydronephrosis and a transplant artery waveform suggestive of increased resistance within the kidney, which resolved in follow-up imaging. As graft function continued to deteriorate, we proceeded with a kidney biopsy on day 13 post-transplant that demonstrated evidence of widespread infiltration of organisms consistent with fungal spores.

A full set of urine and blood cultures were sent for analysis, and the urinary stent was removed. She was immediately started on intravenous anidulafungin after discussion with our microbiologist, but, following a poor tolerance to the therapy, it was changed to intravenous caspofungin and oral fluconazole.

A fluid collection adjacent to the upper pole of the transplanted kidney was noted on repeat ultrasound; this was aspirated and sent for urgent candida culture but revealed no growth. The patient developed a low-grade temperature 3 days later, and a new set of cultures was sent for analysis. On this occasion, urine culture grew citrobacter and...
extended-spectrum beta lactamase, and treatment with temocillin was initiated. Two days later, blood cultures grew *Serratia marcescens* and urine grew *C. glabrata*. The antibiotic regimen was escalated to meropenem and continued with the antifungals.

Further investigations, including vascular Doppler, CT abdomen and transthoracic echocardiogram, were carried out to rule out any IFI-associated vascular complications, but they were all negative for any abnormalities. The patient’s tunnelled dialysis line was removed under aseptic technique after blood cultures were sent.

Our patient received a total of 9 days of antifungal and antibiotic therapy before a decision was made to proceed to transplant nephrectomy. An extensive MDT meeting was held involving the patient, transplant surgeons, transplant nephrologist, the microbiologist and the mycologist. A transplant nephrectomy was performed 23 days after the initial transplant surgery. Amphotericin diluted wash-out was performed intraoperatively.

Following graft removal, the patient continued on antifungals and antibiotics treatment for 2 weeks. A new tunnelled dialysis line was inserted, following two negative blood cultures, for the reinstatement of haemodialysis. She was discharged and placed back on the transplant waiting list.

### INVESTIGATIONS

**Histopathology**

There was evidence of widespread infiltration of small spherical/ovoid organisms which have the appearance of fungal spores. These showed mild variation in size and occasional surrounding halos. The organisms stained positively for periodic acid schiff (PAS) stain, silver stain, Gram and Grocott stains and were present in tubular lumina, tubular epithelium, interstitium and Bowman’s space, but no fungal hyphae were seen. There was associated mixed inflammation involving the interstitium, tubules and surrounding glomeruli, including lymphocytes, histiocytes, neutrophils and eosinophils. (figure 1). The specimen was tested by PCR and it was pan-fungal PCR positive. To further identify the organism, nuclear ribosomal repeat region sequencing identified the organism as *Nakaseomyces glabrata*, previously known as *Candida glabrata*.

Histology of the transplant biopsy comprised of one core of renal cortex with at least 15 glomeruli represented, of which 1 was globally sclerosed. A few glomeruli showed mild mesangial matrix expansion but no mesangial hypercellularity (mm1). A few glomeruli contained capillary neutrophils with focal occlusive neutrophil glomerulitis in one (g1). Glomerular basement membranes appeared normal, with no duplication (cg0).

Interstitial fibrosis and tubular atrophy were difficult to assess, however, there was focal tubular atrophy but no apparent significant fibrosis (ci0, ct1). There was a patchy interstitial mixed inflammatory infiltrate which was neutrophil-rich with some mononuclear cells and scattered eosinophils (i3, ti3). Tubules displayed acute injury with epithelial thinning, cytoplasmic vacuolation and occasional nuclear dropout. Foci of destructive neutrophilic tubulitis were present; however, there was no definite lymphocytic tubulitis (t0). Occasional tubular erythrocytes were present. Arteries showed up to severe intimal fibroelastosis, with no arteritis (v0, cv3). Arterioles displayed mild hyalinosis (ah1). There was no obvious peritubular capillaritis (ptc0). Immunohistochemistry showed quite a lot of serum staining, especially beta-2-microglobulin (BM1). There were no obvious antigens for cytotoxic T-cell (CV0).

Overall, the biopsy demonstrated features consistent with intense fungal spores’ infiltration. The presence of C4d staining and focal neutrophil glomerulitis in this context are of uncertain significance. However, these were considered most likely to be

### Table 1  Parameters and biochemistry results

| Parameters                        | Result        | Reference range |
|-----------------------------------|---------------|-----------------|
| Observations (average)            |               |                 |
| Blood pressure, mm Hg             | 130–180/60–90 | 120/80          |
| Heart rate (beats per minute)     | 90–100        | 60–100          |
| Temperature, °C                   | 36–37.5       | 35–37.4         |
| Urine output, mL/24 hours         | 500–2000 mL/24 hours | – |
| Biochemistry                      |               |                 |
| Creatinine, μmol/L                | 550           | 59–104          |
| Baseline                          |               |                 |
| Average post-transplant           | 330–480       | –               |
| Peak C reactive protein, mg/L     | 90            | 0–10            |
| Average blood glucose, mmol/L     | 10–20         | <7.8            |

**Figure 1  Management of Early Graft Candidiasis in a Kidney Transplant Recipient**

(A) H&E (magnification ×20)—patchy and dense mixed inflammation involving the interstitium, tubules and surrounding glomeruli including lymphocytes, histiocytes, neutrophils and eosinophils. (B) PAS (magnification ×20)—numerous PAS-positive organisms within tubules, the interstitium and in Bowman’s space. (C) PAS (magnification ×40)—numerous organisms within tubules, the interstitium and in Bowman’s space. The organisms are ovoid, showing mild size variation and are intensely and uniformly PAS-positive. (D) Gram stain (magnification ×20)—the organisms stain positively for gram stain. (E) Grocott (magnification ×20)—the organisms stain positively for Grocott stain.
related to the infection rather than true evidence of rejection. That being said, it is difficult to exclude rejection entirely since assessment is somewhat affected by the widespread infection. Banff scores—i3, t0, v0, ti3, g1, ptc0, cg0, ci0, ct1, cv3, mm1, ah1, pv0, C4d2.

Post-transplant nephrectomy histopathology was consistent with the prenephrectomy findings and revealed ongoing fungal infection involving not only the cortex but also the medulla. In addition to the intense fungal infiltration and its associated lymphohistiocytic inflammation, there were focal small cortical abscesses. There was one single artery showing intimal fungal spores.

DIFFERENTIAL DIAGNOSIS
At the early post-transplant stage, the most possible differential diagnoses for DGF are post-ischaemic acute tubular necrosis secondary to the prolonged cold ischaemia time, acute rejection, vascular thrombosis, urinary leak and peritransplant obstructive fluid collection.

The patient was clinically well and haemodynamically stable, which excluded circulatory compromise concerns. Adequate perfusion of the transplanted kidney and exclusion of obstructive uropathy were radiologically confirmed by Doppler scanning and nuclear imaging. The patient continued to struggle with DGF and required renal replacement therapy. We proceeded with graft biopsy to aid the diagnosis. Histopathological examination and assessment confirmed significant fungal infiltration of the transplanted kidney. The specific responsible organism was further identified with nuclear ribosomal repeat region sequencing.

TREATMENT
The patient received 9 days of antifungal therapy guided by regular discussion with the mycologist and the microbiologist. She was also started on antibacterial agents in response to the febrile illness she developed and the subsequent positive urine and blood cultures. The patient was actively mobile post surgery and needed no support in her daily functioning activities. Her glycaemic control was addressed with the help of the diabetic nurse specialist and the duty diabetologist. She underwent surgical nephrectomy of the transplanted kidney 3 weeks post-transplant surgery. The decision to proceed with transplant nephrectomy was discussed in detail in the MDT meeting, and the general consensus was that it was the safest approach to undertake.

OUTCOME AND FOLLOW-UP
The postnephrectomy course was uneventful. The patient completed a further 2 weeks of antifungals as recommended by microbiology and recommenced haemodialysis through a new tunnelled dialysis line following negative blood cultures. She was discharged in good health with a regular thrice weekly outpatient haemodialysis plan and was relisted on the transplant waiting list. She had an arteriovenous fistula vascular access operation but was complicated by steal syndrome. She is now waiting to have the fistula ligated and will continue dialysis through the tunnel dialysis line. Her family is considering donating a kidney through the UK living kidney sharing scheme for the patient to receive a suitable kidney.

DISCUSSION
Donor-derived transmitted infections are rare but can result in devastating outcomes.16–18 There have been a few reports of donor-derived candidiasis occurring in up to 1 in 1000 renal transplants following contaminated perfusion fluid.19 The recipient presentation varies between candidemia, peritransplant collection, infected urinoma or the most significant mycotic aneurysm and its associated anastomotic rupture that can result in significant circulatory collapse and immediate death.20–23 In our rare case, the perfusion fluid was not contaminated but the donor urine grew C. glabrata after a prolonged incubation period during which our patient had a transplant biopsy that highlighted the IFI. Both our patient and the mate kidney recipient grew urinary C. glabrata. The mate kidney struggled with poor function and DGF that necessitated graft biopsy, which revealed features consistent with rejection, but there was no fungal infiltration detected. We believe that our patient encountered an ascending donor-derived urinary fungal infection that infiltrated the grafted kidney during implantation. In addition, the common risk factors for candiduria such as obesity, diabetes mellitus and persistently poor glycaemic control, female sex, urinary catheterisation and immunosuppression status were all present in our case and created a favourable environment for the infection to flourish.24 Our patient should have had her BMI addressed pretransplant and achieved stable and adequate glycaemic control before considering listing her on the deceased donor renal transplantation waiting list. This also applies to premature relisting after discharge following a poor transplant outcome.

Albano and colleagues in a large French multicentre retrospective study that investigated the route of infection for graft site candidiasis described the postinfection clinical presentation and outcomes. In this study, 18 renal transplant recipients had graft candidiasis with variable presentations between fungal renal and/or iliac arteritis being the most common, followed by graft site abscesses, infected urinoma and surgical site infection. Overall, they reported high rates of mortality (16.7%) and morbidity, with 50% requiring surgical graft removal despite optimal antifungal therapy.25 Similarly, in an observational study that assessed candiduria incidence and treatment outcomes in 1223 patients with kidney and kidney-pancreas transplant, Denis and colleagues identified C. glabrata as the most common responsible organism.26 Medical therapy had no significant effect on the fungal clearance rate or the development of serious complications, including death, that were mostly encountered in the first 2 weeks post-transplantation. Furthermore, Mai et al and Rodrigues et al reported cases where the IFI led to fungal arteritis and mycotic aneurysm and, in some cases, resulted in massive bleeding and death. In all cases, patients were receiving antifungal treatment.21,23

The American Society guidelines state that organs from a donor with candidaemia can be used for transplantation but the recipient should receive empirical appropriate therapy.26 The general recommendation is to treat with antifungals for 2 weeks if there is no clinical infection. In the presence of an evident clinical infection, treatment should be extended up to 6 weeks with close clinical, microbiological and radiological monitoring to ensure total eradication of the fungus. Guidance on the optimal management strategy for graft candidiasis and safety to continue with medical antimicrobial therapy versus immediate surgical intervention with transplant nephrectomy is not well supported with strong evidence, and there is a need for precise clarity for optimal antifungal regimes. Infectious diseases guidelines suggest treating patients with candidaemia and IFI with echinocandins and stepping down to oral therapy once the patient’s clinical status stabilises. However, recent studies suggest C.
### Case report

**Patient's perspective**

I was diagnosed with kidney failure 6 years ago on a routine blood test by my GP. They said my kidney function had gone down to about 20%. I was started on steroids, which stabilised my kidneys for a couple of years until it dropped further down to 8%.

I was started on peritoneal dialysis four times a day and every day. It worked for 3 months, but then it began leaking on the inside. I was then sent to the hospital where I was given a central line to start haemodialysis temporarily. I was on the dialysis unit for 4 hours a day, three times a week, and was having to schedule my life around the sessions. I had to retire early from my job. I much preferred peritoneal dialysis as I could manage it myself from home with much more control, even though the haemodialysis made me feel better. After a while, I restarted peritoneal dialysis, but it began leaking again, so I returned to haemodialysis.

I was placed on the transplant list even before I started dialysis. I was excited and nervous about the prospect of getting a new kidney and saw it as my only option for improving my symptoms and my life.

When I came to the hospital for my transplant operation, the nurses were lovely, and I was able to see my daughter and grandson through a glass partition. We [the patients] became a family on the ward, I would help translate medical jargon for the other patients and I keep in touch with them today. It was a big operation, and I suffered some pain, but I felt so much better than I had previously. The doctors came every morning to check on me and update me. They said, ‘your kidney is sleeping and we need to monitor you’. I had few tests and I was reassured, but my kidney function wasn’t improving. They did a biopsy and found a fungal infection. I had two lots of antifungal treatment but wasn’t reacting well to them. I was told that the other kidney recipient had a fungal infection as well. They removed all the plastic (central and dialysis lines) from me, and they called in my daughter so we could have a full update.

The decision to remove my kidney was made very quickly. To me, it felt as if I was on a maternity ward. Every mother was getting to go home with their baby, and mine was being taken away. I think the transplant unit could really benefit from having a counsellor. I think if I was anybody else, I would be suffering from post-traumatic stress disorder from what I went through.

Since having it removed, I have had two fistula operations and developed Steal Syndrome—the symptoms are horrendous. Thankfully, they are planning on tying the fistula off. I am exceptionally protective of my central line now. My diagnosis and complications have brought my family closer together; my niece and sister have offered to enter into the donor swap scheme to ensure I receive a kidney.

Each step of my journey has had its own complications, but I am still looking forward and am hopeful for a transplant in the future.

**Learning points**

- This is a rare case of invasive fungal infiltration with sterile preservation fluid.
- Medical eradication of an invasive fungal infection in transplanted organ can be challenging especially with the antifungal resistance in non-albicans species.
- The wait and see approach in immunosuppressed patients to try to achieve a balance between favourable graft outcome and infection treatment may not be the right choice.
- Early MDT discussion and consideration of removal of the transplanted organ can be life-saving and prevent significant and catastrophic outcomes.

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**glabrata** antimicrobial resistance and less susceptibility to Echinocandin drugs.

Due to the changing trends in the epidemiology of the causative organism, IFIs in the population of transplant recipients continue to be a challenging and complex issue. Despite the fact that IFIs in this cohort are rare, it can be catastrophic if the proper measures are not implemented in a timely manner. We believe that the wait-and-treat strategy with medical therapy in IFI may not be the best option. It can lead to disseminated fungal infection and poor outcomes. In our case, the post-nephrectomy sections showed signs of diffuse fungal infection, small abscesses and early vascular involvement only 23 days after the transplant. This suggests that early intervention with graft nephrectomy can be life-saving.

More studies are needed, as currently there are insufficient evidence-based recommendations to guide clinicians in selecting the best antifungal therapy and escalate care appropriately. We recommend comprehensive and holistic MDT review of biopsy-proven IFI to avoid intervention delay, careful pretransplant recipient screening for transplant candidacy and consideration of IFI as a potential cause of DGF in high-risk patients.

**Contributors** JI and AW wrote the initial manuscript draft and obtained patient consent. GR provided the histopathology images and the initial report. MS was the transplant nephrologist responsible for the patient care with the transplant surgeons, supervised JI and AW, reviewed and redrafted the full manuscript including the histopathology section, reviewed the references, adjusted the journal template as required, reviewed the patient perspective and submitted the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competition of interests** None declared.

**Patient consent for publication** Consent obtained directly from patient(s).

**Provenance and peer review** Not commissioned; externally peer reviewed.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.
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