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Case Report

Post-transplantation cutaneous and renal *Aspergillus* infection

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ABSTRACT

A renal transplant recipient aged 68 years experienced multiple complications after an initial good graft function from a deceased donor transplant. Late in the first week, the patient was oliguric with hematuria; the graft failed in week 2 after the development of a hematoma from a rupture of a renal artery aneurysm. He had a recurrent bleed from the internal iliac graft site and subsequently developed painful dark patches on his leg, distal to where the transplant had been. Histology from the explanted graft and skin biopsies demonstrated *Aspergillus flavus;* this was also grown in the culture of the external iliac artery tissue. Systemic aspergillosis is rare but well recognized, especially in the immunocompromised. Presentations include mycotic aneurysms and secondary cutaneous aspergillosis from hematogenous spread. Diagnosis requires confirmation by histology or direct culture, but a high β-glucan concentration and positive galactomannan antigen can suggest invasive fungal infection in the early stages of the disease. Cases should be managed with systemic antifungals and involvement of local microbiology services; unfortunately, the prognosis is poor.

Case presentation

A male hemodialysis patient aged 68 years underwent a deceased donor renal transplant for end-stage renal disease secondary to diabetic nephropathy. The patient has a history of hypertension, insulin-dependent type 2 diabetes mellitus, asthma, and a metallic aortic valve replacement.

The preoperative immunosuppressive regimen consisted of basiliximab, methylprednisolone, tacrolimus, and mycophenolate mofetil. The patient received a cadaveric graft from a donor aged 38 years, with a 2-1-1 human leukocyte antigen mismatch. The cause of death was intracranial hemorrhage with a history of hypertension. The graft had a good primary function, but on day 4, there was an acute drop in urine output, with a static creatinine, and a Doppler ultrasound demonstrated a well-perfused graft, without hydronephrosis, but absent end-diastolic flow, consistent with acute tubular necrosis (ATN) or rejection. The next day the patient developed hematuria; computerized tomography imaging showed a small hematoma. As the patient was anticoagulated, renal biopsy was deferred and treatment was given for presumed rejection (pulse of 500 mg intravenous methylprednisolone).

On day 6, the patient became breathless with an oxygen saturation of 92% on room air and was admitted to the intensive therapy unit (ITU) for hemofiltration with vasopressor support due to hemodynamic instability. The patient received 7 days of intravenous temocillin and amoxicillin for a presumed hospital-acquired pneumonia. However, the patient's condition deteriorated over the subsequent week, with increasing oxygen and vasosuppressor requirements. Ultrasonography showed a large hematoma compressing and displacing the transplanted kidney, with no vascular flow in the kidney. The patient underwent a graft nephrectomy the same day, retaining part of the donor stump with an aortic patch.

On day 22, the patient once again became hypotensive. A computerized tomography angiogram revealed active bleeding from the external iliac artery at the site of previous anastomosis (see Figure 1a); the patient underwent percutaneous stenting with resolution of extravasation.

Histopathology of the explanted graft revealed a large, pale kidney with several white spots of up to 5 mm in diameter. Microscopy demonstrated areas of inflammation containing neutrophils and multinucleated giant cells, which surrounded fungal hyphae and conidia (see Figure 1b). Fluorescence *in situ* hybridization was positive for fungal and negative for yeast screening. The main renal artery, together with the main renal vein, renal pelvis, and ureter, showed no evidence of fungus. However, the re-

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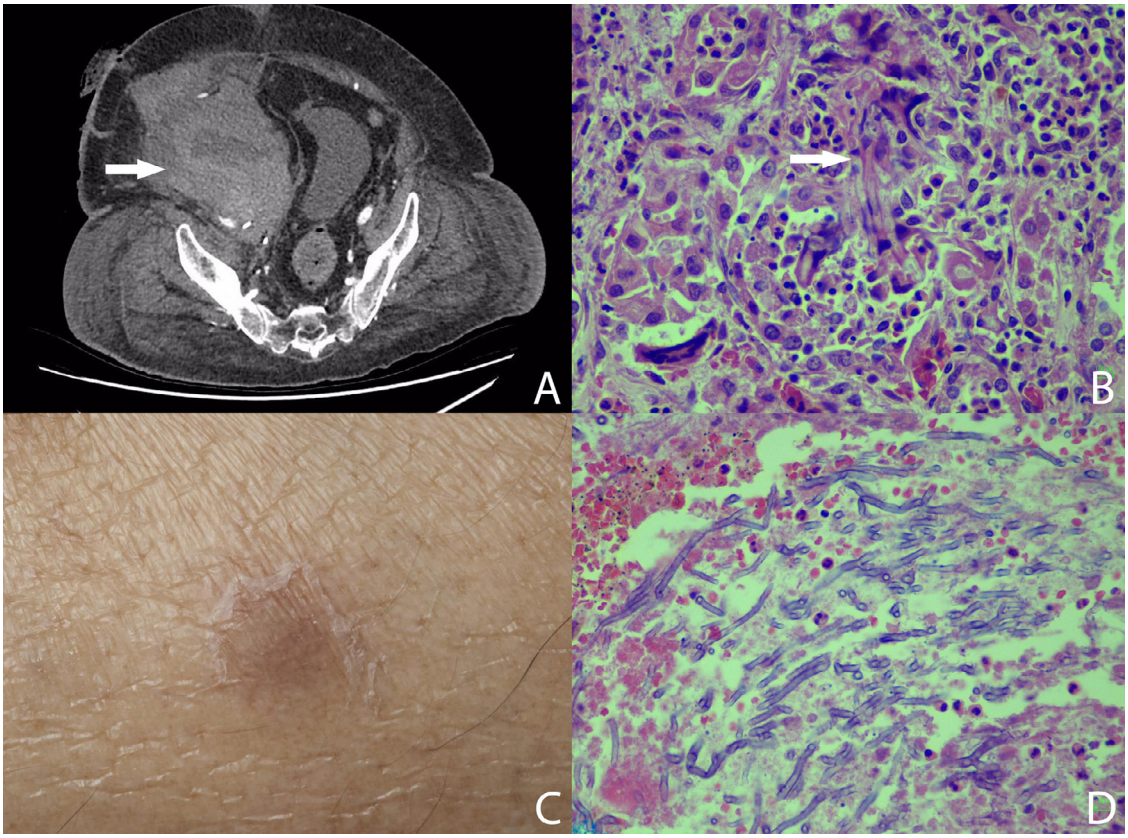

Figure 1. (a): Computed tomography angiogram showing large hematoma arising from renal transplant artery. (b): Histology of renal tissue post nephrectomy showing neutrophils and multinucleated giant cells which surrounded fungal septate, branching, thick hyphae and conidia (indicated). (c): Papular skin lesion on right lower leg. (d): Skin biopsy showing florid fungal hyphae in dermis and subcutis.

nal artery samples grew positive cultures of *Aspergillus flavus*. The patient was started initially on oral voriconazole (400 mg twice daily loading, followed by 200 mg twice daily), and the patient underwent further surgery on day 31 to remove the stent and donor aortic patch (these all subsequently cultured *A. flavus* and vancomycin-resistant *Enterococci*). A femorofemoral bypass procedure was required to preserve the arterial supply to the right leg while fully explanting his donor tissue. Linezolid was added to cover the vancomycin-resistant *Enterococci*, and voriconazole was switched to intravenous delivery, with therapeutic drug monitoring.

Tests for invasive Aspergillus were performed; the β-glucan concentration was >500 pg/l, and galactomannan antigen was detected repeatedly. The diagnosis was made of invasive aspergillosis causing multiple abscesses in the graft, and a perforation of the renal artery at the anastomosis site due to a mycotic aneurysm.

Despite therapy, the patient developed painful dark raised papules on the right lower leg (see Figure 1c). An incisional biopsy of the skin found a suppurative granulomatous inflammation and fungal hyphae (see Figure 1d), with tissue cultures positive for *A. flavus*. Voriconazole was stopped, and a 2-week course of caspofungin 70 mg intravenous once daily was commenced. Further cultures of the peripheral blood, sputum, and central venous catheter were negative for fungal cultures, and a transthoracic echo showed no evidence of a vegetation. The patient continued to deteriorate, this time with a culture-confirmed *Acinetobacter baumannii* pneumonia, which was treated with ertapenem. Sadly, the patient died on day 80 after the transplant. The cause of death after the postmortem examination was listed as multiorgan failure secondary to aspergillosis and end-stage renal failure.

The recipients of the donor's paired renal and islet cell transplants were well at the time of writing, and no cultures grew in the organ preservation fluid.

Discussion

Systemic fungal infections after renal transplantation are well recognized, although not common, with *Aspergillus* being the second most common offending genus after *Candida.* The frequency of invasive aspergillosis in solid organ transplant patients is between 0.5% and 2.2%, most frequently occurring within 6 months of transplantation, and unfortunately, as in this case, it is usually fatal (case fatality rate up to 88%) [1]. In addition to general risk factors for fungal infection, such as immunosuppression, our case had nearly all the predisposing factors for early *Aspergillus* infection after transplantation identified by López-Medrando *et al.* [2]; preexisting diabetes mellitus, pretransplant requirement for chronic hemodialysis, use of vasopressors postoperatively, admission to the intensive care unit, concurrent bacterial bloodstream infection, and delayed graft function. We note with interest that this case-control series also identifies pretransplant chronic obstructive pulmonary disease as a risk factor and reflect that the asthma diagnosis in our case could have been explored further. Regarding this patient's skin involvement, superficial fungal skin infections after solid organ transplants are actually relatively common, for example, with Candida species. Deeper, soft tissue infections are rarer, with a higher incidence in the first months after transplantation, as in this case. Cutaneous aspergillosis can either be primary or secondary in origin, with primary infection being more common. Secondary cutaneous lesions may present as either the result of contiguous

extension of infection from underlying tissues to the skin or the widespread dissemination of blood-borne fungus, which was the mechanism of spread in this case.

Due to the high fatality rate and the frequently occult nature of early disease, diagnosing systemic aspergillosis in a solid organ transplant recipient is both necessary and difficult, as demonstrated by the delayed diagnosis in this case. Culture is notoriously unreliable. Because *Aspergillus* reproduces in host tissues, it releases the cell wall component galactomannan; hence, the serum galactomannan enzyme-linked immunosorbent assay is a specific diagnostic technique for invasive *Aspergillus* infection. Measured sequentially, galactomannan can also be a good predictor of treatment and survival; although, it is not very sensitive [3]. Serum assays for $(1 \rightarrow 3)$-β-D-glucan, a fungal cell wall antigen, are often paired with galactomannan testing but are not specific for *Aspergillus*. Definitive diagnosis from tissue biopsy with antifungal staining and molecular fungal identification remains the gold standard. Differential diagnoses include Fusarium species and Zygomycetes. The dark raised papules observed in the right leg of our patient are the probable result of fungal emboli originating in the ipsilateral renal artery mycotic aneurysm. Vascular complications are rare; although, transplant artery mycotic aneurysms due to Aspergillus, resulting in a hemorrhage have been reported [4].

The primary origin of infection in our case remains unclear, a not uncommon conundrum [5]. The portal of *Aspergillus* entry is usually the respiratory tract; however, the patient had no pulmonary symptoms: sputum cultures were negative and he had no changes on his chest radiograph before his final readmission to the intensive care unit. No other transplant recipients from the same donor had any Aspergillus infections. Other possible sources of infection include Aspergillus colonization of the recipient himself and contamination of the perfusion fluid, the allograft, or the intraoperative environment. No other cases have been reported at this unit.

The Infectious Diseases Society of America recommends an initial treatment with voriconazole [6], which has the largest evidence base. The options for salvage therapy include amphotericin, posaconazole, itraconazole, caspofungin, or micofungin. Voriconazole levels should be monitored; after an initial supratherapeutic level of 7.13 mg/l, our patient was maintained in the target range of 1-5.5 mg/l. If possible, the infectious focus should be surgically resected and impaired host defenses should be restored by reducing immunosuppression.

Learning points from this case include, unfortunately, the difficult discussion about which patients should not be considered fit for transplantation due to their comorbidity. A scoring system for the risk of early invasive aspergillosis has been proposed [2], which could assist in this, but it is not routinely practiced. With a trend toward transplantation in comorbid patients, early consideration of fungal infection is vital. At present, antifungal prophylaxis before surgery is not routine. A high index of suspicion, together with regular screening, remains essential for early detection and treatment.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

Every effort has been made to anonymize the case.

Author contributions

ERW, SAE and SBW devised the paper. ERW and SAE wrote the manuscript; SBW revised and approved the final draft

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