

# Pacemaker-related *Candida parapsilosis* fungaemia in an immunosuppressed renal transplant recipient

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## SUMMARY

Renal transplant recipients are at risk for opportunistic infections due to their immunosuppressed state. We describe the case of a 59-year-old renal transplant recipient who presented with sepsis and bilateral pulmonary emboli due to *Candida parapsilosis*. She was treated with intravenous caspofungin and had a transoesophageal echocardiogram, which revealed vegetations on her pacemaker leads. She then underwent surgery to replace her pacemaker; however, her blood cultures remained positive for *C. parapsilosis* postoperatively. Her antifungal was switched to liposomal amphotericin B and flucytosine for 6 weeks, which yielded sterile blood cultures, and she was then initiated on lifelong fluconazole. Her recovery was complicated by tacrolimus toxicity 1 month after discharge due to fluconazole-induced CYP3A inhibition.

## BACKGROUND

Kidney transplant is the accepted therapy for many cases of end-stage renal disease, with improving survival and allograft function over the years.<sup>1</sup> Due to immunosuppressive treatments, these patients remain at high risk for opportunistic infections. In particular, they are at increased risk of invasive fungal infections (IFIs), with an incidence of 3.1% in all transplant recipients and 1.3% in renal transplant recipients<sup>2</sup>; *Candida* spp account for the majority of these IFIs. IFIs are associated with high morbidity and mortality and require early diagnosis and treatment. We describe a case of a renal transplant recipient who developed *Candida parapsilosis* fungaemia with infected pacemaker leads and required a prolonged hospital admission to manage it.

## CASE PRESENTATION

A 59-year-old woman presented to the emergency department with fever and progressive dyspnoea for the preceding 5 days, and general malaise over the preceding month, with a 2 kg weight loss. Normally a very attentive patient, she delayed seeking medical attention due to concerns attending hospital during the COVID-19 pandemic. She had a complex background medical history, including end-stage renal disease secondary to type 1 diabetic nephropathy. She had undergone a successful simultaneous pancreatic kidney transplant in 1993, with allograft kidney failure in 2010. She received haemodialysis until 2016 when she received a deceased kidney donor transplant. She also had a pacemaker in situ for complete heart block that had been replaced 1.5 years prior with a St. Jude's pacemaker with

right atrial and right ventricular leads. She was also diagnosed with breast cancer in 2011, treated with mastectomy and lymph node clearance, for which she remained on tamoxifen.

## INVESTIGATIONS

Her blood results showed an elevated D-dimer at 40.57 µg/mL, and a subsequent CT pulmonary angiogram confirmed bilateral subsegmental pulmonary emboli. She was started on therapeutic enoxaparin, and her tamoxifen was stopped. Her C reactive protein was also elevated at 78 mg/L, and she had an acute kidney injury with a creatinine of 270 µmol/L from a baseline of 60–70 µmol/L, felt to be secondary to sepsis. Her blood pressure was very labile, requiring midodrine therapy. She was started on piperacillin–tazobactam for empirical antimicrobial cover, and her tacrolimus and mycophenolate mofetil were held; however, 40 hours after incubation, her blood cultures grew *C. parapsilosis*. Two subsequent blood cultures confirmed the same diagnosis. She was started on intravenous caspofungin, had an ophthalmological examination, which ruled out intraocular candidiasis and had a transoesophageal echocardiogram to search for the source of the fungaemia. This revealed three vegetations of 1.5–2 cm on the right ventricular lead of her pacemaker, with moderate tricuspid valve obstruction. The pacemaker pocket itself did not appear clinically infected.

## TREATMENT

Her case was discussed with the cardiothoracic surgery department, who agreed she needed rapid removal of her pacemaker leads. While waiting for surgery, she developed features of disseminated intravascular coagulation. The low molecular weight heparin was switched to unfractionated heparin because of ongoing poor renal function. She had a peripherally inserted central catheter (PICC) placed due to difficult venous access, and 48-hourly blood cultures continued growing *C. parapsilosis*.

Two weeks after her initial presentation, she underwent a midline sternotomy with removal of four pacing leads and tricuspid valve vegetations, as well as a patch repair and annuloplasty for septal leaflet perforation. An epicardial pacemaker was inserted to manage her complete heart block. Her PICC was also changed. In total, she required 7 units of red cells, 8 units of fibrinogen and 2 pools of platelets. Her postoperative echocardiogram showed good cardiac function, with an ejection fraction of 55%.



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Her caspofungin was continued and repeat blood cultures showed persistence of the candidemia. The differential diagnosis at this point was either PICC line or native tricuspid valve related persistence of *C. parapsilosis*. Her PICC was removed and sent for culture and remained sterile. A new line was inserted after 24 hours; however, despite this, her blood cultures remained positive for *C. parapsilosis*. Her pacemaker leads had been sent externally for susceptibility testing and revealed sensitivities to:

- ▶ Amphotericin B, with minimal inhibitory concentration (MIC) of 0.25 units.
- ▶ Caspofungin, with MIC of 0.5 units.
- ▶ Fluconazole, with MIC of 1.0 units.

As per the Infectious Diseases Society of America 2016 guidelines,<sup>3</sup> she was switched to intravenous liposomal amphotericin B, a formulation with reduced nephrotoxicity compared with amphotericin B, and oral flucytosine was added. Her transesophageal echocardiogram was repeated and showed echodensities on the tricuspid valve, which were stable after 1 week, and no obvious vegetations.

Finally, 5 weeks after admission and 3 weeks after her surgery, the blood cultures became persistently sterile. She was discharged home and received a total of 6 weeks of combination antifungal therapy from the time of her first sterile blood culture.

## OUTCOME AND FOLLOW-UP

Following these 6 weeks, she was started on lifelong oral fluconazole to maintain antifungal coverage. She was monitored weekly as an outpatient, including her tacrolimus level and renal function, which improved progressively.

One month after discharge, she presented with confusion, falls at home, low mood and anorexia. Her CT of the brain showed no acute changes, but her tacrolimus levels were significantly elevated at 42 ng/mL. She also had an acute kidney injury, with a creatinine of 463  $\mu\text{mol/L}$ , and had a raised white cell count of  $20.4 \times 10^9$  cells/L. Her midstream urine sample showed a urinary tract infection. Her tacrolimus was held to treat the tacrolimus toxicity, and she was prescribed 7 days of ciprofloxacin which cured her urinary infection, and she was discharged home. She was seen back in the nephrology clinic 7 months after her initial presentation to hospital, with her creatinine back to her baseline of 60–70  $\mu\text{mol/L}$ , and her mycophenolate mofetil was finally restarted. By this time, she was feeling extremely well.

## DISCUSSION

Immunosuppressed patients are at increased risk of community and hospital acquired infections, including fungal infections of which invasive candidiasis is the most prevalent.<sup>4</sup> Indeed, infections remain the second most common cause of death (after cardiovascular disease) in these patients.<sup>5</sup> Candidemia presents with vague and non-specific symptoms and needs to remain within the differential of any patient presenting with sepsis, particularly in high-risk patients such as renal transplant recipients presenting with persistent fever despite adequate antimicrobial treatment. IFIs account for up to 5% of all renal transplant recipients' infections.<sup>6</sup> *Candida albicans* remains the leading cause of candidiasis; however, over the past few years, its incidence has been decreasing while non-*albicans* *Candida* species are becoming more prevalent.<sup>4</sup> Of these, *C. parapsilosis* represents the second or third most common *Candida* spp, depending on the country.<sup>4</sup> It carries a lower morbidity and mortality compared with *C. albicans*,<sup>4</sup> with a mortality estimated in some studies to be around 40%.<sup>7</sup> Predisposing risk factors to *C. parapsilosis* include the presence of prosthetic

cardiac valves, intravenous drug use, immunosuppression and solid organ transplant recipients.<sup>8–10</sup> *C. parapsilosis*' ability to adhere to medical implanted devices and form biofilms contribute to its virulence<sup>4</sup> and its ability to infect implanted cardiac devices.

Blood cultures allow the diagnosis of *C. parapsilosis* and allow testing for susceptibility to different antifungal agents. Investigations to find a source are crucial to properly manage candidaemia and should include a transthoracic or transoesophageal echocardiogram. Any intravenous access such as central venous catheters should be removed and sent for cultures and sensitivities as these could be the source of *C. parapsilosis*.

If an implanted cardiac device is identified as being the source of infection, both the European Society for Cardiology and the Infectious Disease Society of America (IDSA) strongly recommend removing this device<sup>3 11</sup> and treating the fungaemia with antifungal agents. A recent systematic review found that in cases of fungaemia in the presence of implantable cardiac devices, extraction of the devices was associated with both increased survival to discharge and increased clinical recovery or cure.<sup>12</sup> In the case of native valve endocarditis, the IDSA recommends the use of lipid formulation amphotericin B with the addition of flucytosine in certain cases, or treatment with high dose echinocandins, such as caspofungin. Amphotericin B is a polyene antifungal with a broad spectrum of activity that has been associated with nephrotoxicity<sup>13</sup> and other side effects in up to 50% of cases.<sup>6</sup> For this reason, it should not be used as a first-line agent, in particular in a renal transplant recipient. The liposomal formulation not only has fewer renal adverse effects,<sup>14</sup> but it also has a reduced all-cause mortality<sup>15</sup> and a higher efficacy<sup>16</sup> compared with amphotericin B.

There are no clear guidelines regarding the duration of antifungal therapy in renal transplant recipients with an IFI. Previous guidelines have advised that long-term suppressive fluconazole therapy may be warranted following fungal endocarditis where prolonged intravenous therapy was required,<sup>17</sup> and that this may even be lifelong if surgical management is not possible. Prophylactic fluconazole has been shown to decrease the incidence of IFIs in liver transplant patients, although not in renal transplants.<sup>18 19</sup> Fluconazole prophylaxis was also associated with higher rates of calcineurin inhibitor toxicity.<sup>19</sup> There have been few reported cases of pacemaker-related fungal endocarditis,<sup>20</sup> and to our knowledge, none where the patient was a solid organ transplant recipient. However, considering our patient's prolonged infectious course and her susceptibility to IFIs, the decision was made to prescribe lifelong fluconazole therapy.

The interactions between the calcineurin inhibitor tacrolimus and fluconazole are clinically important. Some studies have shown that the combination of tacrolimus and azole antifungal agents has a synergistic effect in treating *Candida* spp, both in vitro and in vivo, and particularly in the case of resistant *Candida* spp.<sup>21–23</sup> Calcineurin inhibitors make fluconazole fungicidal, not fungistatic, and the disruption of *Candida* spp cell membrane by fluconazole leads to increased intracellular levels of calcineurin inhibitors, leading to cell death.<sup>22</sup> Fluconazole also inhibits CYP3A4/3A5 which impairs the hepatic metabolism of tacrolimus.<sup>24</sup> For this reason, patients on both fluconazole and tacrolimus are at high risk of tacrolimus toxicity.<sup>24</sup> The Food and Drug Administration recommends that close monitoring of tacrolimus pharmacokinetics should be performed while on fluconazole therapy.<sup>25</sup> Some studies have also recommended reducing the dose of tacrolimus by up to 56% when starting fluconazole.<sup>24</sup> Our strategy is to judiciously reduce the tacrolimus dose, monitor trough levels closely and monitor the

patient closely for signs of tacrolimus toxicity, such as acute kidney injury, tremor, headache and seizures.<sup>26 27</sup>

Our patient's late presentation to the hospital illustrates a larger issue that has confronted physicians and healthcare systems during the COVID-19 pandemic. There are accumulating reports of reduced admissions with acute coronary syndromes,<sup>28 29</sup> strokes and transient ischaemic attacks,<sup>30</sup> and other emergencies, such as subarachnoid haemorrhages.<sup>31</sup> During the COVID-19 pandemic, the number of out-of-hospital cardiac arrests doubled in Paris, France, compared with the previous year. Only a third of this increase could be attributed to COVID-19 infection.<sup>32</sup> This reluctance to attend hospital is presumably due to the perceived risk of being an inpatient (or even outpatient) and contracting COVID-19. To minimise such delays in presentation, patients need to be reassured that infection control measures are applied in hospital to minimise their risk of contact with COVID-19, and they need to be reminded that they should continue to seek medical attention if they feel unwell.

This case highlights the importance of rapid diagnosis and management of sepsis in an immunosuppressed patient with appropriate antimicrobials, including antifungal agents where appropriate. Future trials and guidelines on the optimal duration of treatment of fungal endocarditis in renal transplant recipients and on the dosing of tacrolimus when coprescribed with fluconazole would improve patient care.

### Learning points

- ▶ In any immunosuppressed patient presenting with sepsis, clinicians need to maintain a high index of suspicion for fungal infections, particularly if they are not responding to broad-spectrum antibiotics.
- ▶ In a patient with not only pulmonary embolism, but also signs of sepsis the possibility of septic (rather than thrombotic) emboli should be considered.
- ▶ Tacrolimus trough levels should be closely monitored in acutely unwell patients, and particular attention should be directed towards potential drug interactions, which increase the risk of tacrolimus toxicity.
- ▶ Interdisciplinary work in complex cases such as this improves patient care and management.
- ▶ Despite the COVID-19 pandemic, patients should be reminded to attend the hospital for medical care when they are acutely ill.

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