CASE REPORT

Disseminated *Mycobacterium tuberculosis* following renal transplant with alemtuzumab inductionAdam Baghban,¹ Marwan Mikheal Azar,² Raffaele Mario Bernardo,¹ Maricar Malinis^{1,3}¹Department of Internal Medicine, Section of Infectious Diseases, Yale University School of Medicine, New Haven, Connecticut, USA²Department of Pathology, Section of Microbiology, Massachusetts General Hospital, Boston, Massachusetts, USA³Department of Surgery, Section of Transplantation, Yale University School of Medicine, New Haven, Connecticut, USA

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SUMMARY

Mycobacterium tuberculosis presents unique challenges in the peritransplant period. Here, we describe a case of disseminated tuberculosis following renal transplantation with alemtuzumab induction immunosuppression in a patient with remotely treated pulmonary tuberculosis and ongoing risk factors for re-infection. We also review the available literature regarding the prevalence of tuberculosis infection following solid organ transplant and management of high-risk patients, including the role for isoniazid preventative therapy.

BACKGROUND

Mycobacterium tuberculosis (TB) is an important cause of post-transplant infection. The risk of active tuberculosis is 20–74 times higher in solid organ transplant (SOT) recipients compared to the general population.^{1–2} Such cases have been associated with a mortality of 6–31% compared to <5–6% in the general population.^{3–4} Disseminated and extrapulmonary disease have been found to account for up to 23–67.4% of tuberculosis in SOT, whereas only 5–20% of non-transplant, non-HIV-related TB is extrapulmonary.^{5–7}

Despite the increased risk of active TB, with its associated morbidity and mortality among SOT recipients, available screening assays are inherently limited. Donor and recipient assessment for latent TB relies on indirect measures of TB exposure such as tuberculin skin testing or interferon gamma-release assays (IGRAs). These tests rely on an adequate cellular immune response, which is often lacking in patients with end-stage organ failure.⁴ Supporting this statement, the rate of indeterminate QuantiFERON-TB-Gold IGRAs has been shown to be increased in multiple chronic medical conditions, including chronic renal failure.⁸ Patients with a history of treated tuberculosis prior to SOT pose an additional challenge, as immunological testing cannot distinguish between latent and cured disease, thus limiting the assessment to surveillance of symptoms and imaging to evaluate for active TB.

In non-transplant patients residing in North America, recurrence of treated tuberculosis is rare, estimated at 3.71%. Most of these cases (3.59%) represent relapse rather than new infection.⁹ In contrast, among patients with renal transplant in France, another low prevalence region, 18.4% of tuberculosis cases occurred in patients with a history of treated tuberculosis, indicating that previously treated TB is a significant risk factor in this population.⁵ Patients with previously treated TB may

represent a high-risk group which warrants regimented surveillance in the first year post-transplant. Additionally, the use of isoniazid (INH) prophylaxis post-SOT has been studied in endemic regions.^{10–11} However, extrapolation of these findings to patients in low-prevalence regions is based on expert opinion and the clinician's individualised risk assessment.¹² Here, we present a patient with significant TB risk factors and a history of remotely treated pulmonary TB, who developed disseminated TB during her fourth month following renal transplant.

CASE PRESENTATION

A 74-year-old woman with a history of end-stage renal disease secondary to diabetes mellitus and contrast nephropathy, who had been on peritoneal dialysis for 4 years, was evaluated by the infectious diseases service 97 days after deceased donor renal transplantation (CMV D+/R+, EBV D–/R+) with progressive left neck swelling and fever. Her history was notable for multiple TB risk factors: she was born in the Philippines, worked in health-care and was remotely treated for active pulmonary TB while in the Philippines. Details of her previous treatment were unavailable. Pretransplant evaluation included positive tuberculin-skin testing and a chest X-ray that was without evidence of infiltrate, granulomas or adenopathy. She did not have a pre-transplant infectious diseases evaluation. Adding to her overall infectious risk, her pretransplant haemoglobin A1c was 8.9. She received alemtuzumab and a methylprednisolone taper as induction immunosuppression, along with mycophenolate 1 g two times per day and tacrolimus 4 mg two times per day for initial maintenance immunosuppression. Antimicrobial prophylaxis included trimethoprim-sulfamethoxazole (TMP-SMX), fluconazole and valganciclovir. She developed delayed graft function, with intermittent peritoneal dialysis, and eventual normalisation of her renal function. A renal biopsy did not show evidence of acute rejection at 2 months post-transplant. She was transitioned to belatacept (5 mg/kg every 2 weeks) after she developed tacrolimus nephrotoxicity. *Pneumocystis jirovecii* prophylaxis was changed from TMP-SMX to dapsone due to renal impairment.

Her post-transplant course was significant for multiple infectious complications. At 5 weeks post-transplant, she was admitted with influenza A pneumonia and *Clostridium difficile* colitis. Through her first 3 months post-transplant, she had multiple admissions with recurrent *C. difficile* associated diarrhoea and carbapenem-resistant *Klebsiella*

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pneumoniae and vancomycin-resistant *Enterococcus* urinary tract infections. She developed *Candida glabrata* pyelonephritis of the transplanted kidney with associated candidemia and hydronephrosis requiring percutaneous nephrostomy. She received anidulafungin intravenously and amphotericin B irrigation via her nephrostomy tube for 14 days.

At 4 months post-transplant, she developed intermittent fever (up to 39°C) and left neck swelling at the site of her internal jugular central line. The line was removed, and the neck mass was incised and drained by interventional radiology. CT of the neck with contrast showed cystic rim enhancing complex masses involving the left lateral cervical soft tissues and right paratracheal space worrisome for abscesses (figure 1), in addition to bilateral patchy upper lung consolidations (figure 2). Further drainage and tissue biopsies were pursued based on her imaging. Ziehl-Neelsen staining of wound drainage revealed acid-fast bacilli. Nucleic acid amplification testing confirmed the presence of rifampin-sensitive *Mycobacterium tuberculosis*, and rifampin, pyrazinamide, ethambutol and isoniazid (RIPE) were initiated. Regarding her immunosuppressives, mycophenolate was already held in the setting of fevers, and a dose of belatacept was postponed by 1-week in the setting of her diagnosis of disseminated TB. Respiratory gram stain confirmed the presence of acid-fast bacilli and respiratory cultures grew TB within 5 days of collection. Histopathology of the neck lesions showed abscesses with extensive necrosis, acute and chronic inflammation and granulation tissue formation (figure 3). The TB isolate was sensitive to RIPE, and ethambutol was discontinued after 1-month of therapy. Pyrazinamide was discontinued after 2 months of therapy. Rifampin and INH were continued for 12 months total. She remains well and without relapse at the time of this publication.

Of note, IgG was 724 mg/dL 1-month post-transplant and 933 mg/dL 3 months post-transplant. A T-cell subset was checked 4 months post-transplant and revealed a CD4 count of 18/ μ L and a CD8 count of 77/ μ L. These tests were repeated at 6 months and revealed a CD4 count of 313/ μ L and a CD8

Figure 1 CT soft tissue neck with contrast. A complex, multiseptated, rim-enhancing cystic mass in the left lateral cervical soft tissues posterior to the angle of the mandible.

Figure 2 CT soft tissue neck with contrast. A cystic mass within the right paratracheal space displaces the esophagus to the left and measures 2.5x3.5 cm. Patchy consolidations of the bilateral upper lung fields are also seen.

count of 857/ μ L. She has not suffered infectious complications following recovery of her T cells.

DISCUSSION

The current report describes the case of a foreign-born patient with renal transplant induced with the anti-CD52 monoclonal antibody alemtuzumab, who developed disseminated tuberculosis at 4 months post-transplantation. The patient's grossly depressed CD4 T-cell counts and recurrent opportunistic infections (OI) with *Candida* and *C. difficile* were indicative of her profoundly immunosuppressed state.

Alemtuzumab use has been correlated with a significantly increased risk of OI related to a dose-independent impairment of cell-mediated immunity, which can persist for over 9 months after administration.¹³ Although not the most common post-transplant infection, TB post-alemtuzumab has been well documented, especially in highly endemic areas such as Asia. In a retrospective analysis of 182 Asian patients who received the drug to treat haematological disorders, 16 cases of TB were observed.¹⁴ As with our patient, median time to infection was rapid, at 4 months, with a range of 1–24 months. This rapidity is suggestive of reactivation as opposed to primary infection. Most of these cases were pulmonary, but three cases of TB meningitis were identified. Similarly, use of alemtuzumab for haematological malignancies in Hong Kong had a 1-year and 2-year

Figure 3 Soft tissue, left neck abscess. Abscess formation and extensive necrosis with acute and chronic inflammation and granulation tissue formation.

reactivation risk of 31% and 45%, respectively.¹⁵ The high incidence of active TB in these studies is not surprising given that they were conducted in regions with a high TB prevalence. It is also possible that the included patients were more severely immunosuppressed due to their underlying haematological disorders. In contrast, induction immunosuppression with either antilymphocyte globulin (ATG) or anti-CD25 monoclonal antibodies in patients with renal transplant in southern China was associated with a 1.76% incidence of active TB, and somewhat higher at 5.2% in another southern Chinese population of patients with renal transplant.^{16 17}

Studies in low prevalence regions suggest a much lower incidence of active tuberculosis following SOT with alemtuzumab induction. One such study, conducted in the UK, observed only one case of tuberculosis among 33 renal transplant recipients with alemtuzumab induction over 5 years.¹⁸ Similar to our patient, this reported case of TB following alemtuzumab occurred in an immigrant from the Philippines who did not receive INH prophylaxis post-transplant. In another study, conducted in Pittsburgh, only one case of active TB was identified of 547 patients who received alemtuzumab for induction immunosuppression.¹⁹ Finally, a small study out of South Korea, which has an intermediate TB prevalence, identified one case of pericardial TB of 11 patients receiving alemtuzumab induction for kidney transplantation.^{20 21} These findings highlight the significance of epidemiological risks for TB and those afforded by profound immunosuppression. On the other hand, the benefit of lymphocyte-depleting agents is a decreased risk of acute rejection and the potential for steroid avoidance after the initial induction period, which was the case with our patient.²²

Our patient reported multiple epidemiological risk factors for tuberculosis. She was born in the Philippines and reported prior treatment for tuberculosis. Previously treated tuberculosis is associated with an increased risk of active tuberculosis post-transplant possibly due to persistence of tuberculous bacilli despite clinical cure.²³ Our patient reported visiting the Philippines yearly since her immigration to the USA. Furthermore, subsequent to her immigration, she pursued a career as a healthcare worker. Therefore, in addition to the possibility of relapse, re-infection should be considered. A study from Italy identified a fourfold increased risk of re-infection among immigrants from high prevalence countries, confirmed by DNA fingerprinting of the second, different, TB isolate.²⁴ Advanced age at the time of transplant has also been identified as an additional risk factor for active TB following SOT, possibly due to age-related reductions in cellular immunity.^{2 25} Additionally, diabetes mellitus has been shown to be associated with increased risk for tuberculosis following SOT.²⁵ On the basis of these risk factors, our patient warranted close monitoring and maintenance of a high index of suspicion for development of active tuberculosis. Furthermore, she may have benefited from a pretransplant infectious diseases evaluation for risk assessment and mitigation. Of note, in SOT recipients with active TB, fever is the most common symptom, between 64% and 91% of cases,²⁶ as was the case with our patient at the time of diagnosis.

The use of chemoprophylaxis in high-risk SOT recipients is incompletely defined, but studies have begun to shed light on its merit. INH preventative therapy was found to reduce mortality in HIV patients in Sub-Saharan Africa.^{27 28} Currie *et al*¹⁰ performed a comprehensive review of observational and randomised controlled trials (RCT) of INH prophylaxis use in SOT recipients. All of the RCTs reviewed took place in South Asia and involved renal transplant recipients. The focus of these studies was on INH as a preventative therapy rather than latent TB treatment. Screening for latent TB was either not pursued,

or patients were randomised independent of prior testing. Duration of INH therapy was typically 1-year post-transplant, which is when the risk of development of active TB is greatest.⁴ Meta-analysis of the four randomised-controlled trials revealed a relative risk (RR) of TB infection of 0.31 in patients receiving INH post-transplant, without significantly increased risk of drug-induced hepatitis. Similarly, a Cochrane review found a RR of 0.35 when INH was given to patients with renal transplant in high prevalence regions; however, this was offset by a RR of liver damage of 2.74.¹¹ Application of these data to patients residing in low-risk areas is challenging. While generalised use of isoniazid (INH) preventative therapy in low prevalence regions would involve exposing patients to unnecessary medications and increased pill burden without universal benefit, subpopulations with significant risk factors may benefit from this therapy. Further studies are necessary to better define patient criteria that warrant preventative INH in such regions.

Learning points

- ▶ Careful risk assessment through obtaining a thorough exposure history, including a history of prior TB treatment, is a critical component of the pretransplant evaluation.
- ▶ Among patients with significant risk factors, surveillance in the form of symptom assessment and imaging are warranted post-transplant, along with maintenance of a high index of suspicion for development of active TB.
- ▶ Lymphocyte-depleting agents such as alemtuzumab should be used with caution in patients with significant risk of TB re-activation.
- ▶ Isoniazid (INH) prophylaxis may be of benefit, extrapolating from studies of SOT patients in TB endemic regions.¹⁰
- ▶ Further studies of INH preventative therapy in high-risk patients residing in low prevalence regions may help identify risk factors that can shape guidelines for INH use post-SOT in the future.

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