



Diagnostic and therapeutic challenges of tuberculosis in kidney transplant recipients; a case series study

Siti Nur Rohmah^{1*}, Metalia Puspitasari¹, Yulia Wardhani¹, Nur Rahmi Ananda², Alfreda Amelia Khotijah³

¹Nephrology and Hypertension Division, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

²Pulmonology Division, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

³Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

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ABSTRACT

Introduction: One of the most serious bacterial infections following kidney transplantation is tuberculosis (TB). Immunosuppressive medications and anti-tuberculosis therapy (ATT) frequently interact with one another and cause adverse effects. This case series focuses on kidney transplant patients who have active TB, with varying clinical manifestations and outcomes.

Case-1: A 42-year-old man with end-stage renal disease (ESRD) underwent a kidney transplant from an unrelated living donor. He was diagnosed with disseminated TB post-transplant. Third-month post-ATT, serum creatinine was increased. His kidney allograft failed and required hemodialysis, but he died.

Case-2: A 31-year-old female with ESRD underwent a kidney transplant from an unrelated living donor. She was diagnosed with pulmonary TB post-transplant. Third-month post-ATT, her tacrolimus decreased significantly; however, her kidney allograft remained stable and still alive.

Case-3: A 29-year-old male with ESRD underwent a kidney transplant from an unrelated living donor. He was diagnosed with pulmonary TB post-transplant. Third-month post-ATT, tacrolimus levels decreased significantly but her kidney allograft remained stable.

Case-4: A 60-year-old man with ESRD underwent a kidney transplant from an unrelated living donor. He was diagnosed with Disseminated TB post-transplant. Third-month post-ATT, tacrolimus levels decreased significantly since, her kidney allograft remained stable.

Conclusion: After kidney transplantation, TB might be difficult to diagnose and treat because of its unusual symptoms and varying outcomes. During the first three months of ATT, there may be significant interactions between tacrolimus and ATT. Therefore, frequent and careful monitoring along with medication modifications are required. Tuberculosis prophylaxis is essential for recipients after transplantation, particularly in endemic countries.

Implication for health policy/practice/research/medical education:

Tuberculosis (TB) infection after kidney transplantation with immunosuppressant drugs is still underreported and remains a challenge in both diagnosis and therapy. We present several cases of TB infection after kidney transplantation with unusual symptoms and differing clinical outcome. The existence of interactions between ATT and immunosuppressant treatment requires special attention to avoid kidney allograft failure and rejection. It is important for clinicians and policymakers especially in endemic countries to be aware of these interactions and to take necessary precautions for the diagnosis and management of TB in kidney transplant recipients.

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Introduction

The frequency of tuberculosis (TB) among recipients of solid organ transplants is considered underreported (1).

Active TB is one of the world's top 10 causes of death by *Mycobacterium tuberculosis* (2). The case percentage of active TB is estimated to be between 1.2%-6.4% in

*Corresponding author: Siti Nur Rohmah, Email: siti.nur.r@ugm.ac.id

developed countries and up to 15% in endemic areas (1), with a 6-22% mortality rate regardless of treatment (3,4). As many as 15% of post-transplant TB cases have advanced extrapulmonary TB with a mortality rate of 30%. TB infection in immunocompromised patients, such as kidney transplants on immunosuppressant drugs, often presents with atypical and chronic symptoms, leading to delayed diagnosis and treatment (4). We report four cases of active TB in recipients of kidney transplants, each with a unique clinical presentation and course of treatment. It is intended that these four cases will serve as an overview for physicians, helping them to remember how to diagnose and treat TB in kidney transplant recipients as well as the several risk factors that can impact the survival of renal allografts in patients with TB.

Objectives

This case series study aims to present 4 cases of post-kidney transplant infection with varying clinical symptoms and therapy.

Case Series

This study reports four patients (three males and one female) with a mean age of 40 ± 25 years old. All cases had different clinical presentations and outcomes. Two cases were TB infection with lung involvement, one case with TB disseminated (TB lung and skin), and the other case was TB pleura. The diagnosis and management of each patient were different too.

Case I

A 42-year-old, Javanese male, suffered from chronic kidney disease presumed secondary to hypertension since 2013 and had been undergoing hemodialysis for 7 years. The patient underwent a kidney transplant in October 2020 from an unrelated living donor with HLA matching 2/16 (HLA C*07:01 and HLA DPA1*02:01), negative virtual crossmatch, and negative complement-dependent cytotoxicity (CDC) crossmatching. He received induction with 125 mg methylprednisolone (iv), 720 mg mycophenolic acid tablet, 0.06 mg/kg weight tacrolimus, and 20 mg basiliximab. He was maintained on tacrolimus, mycophenolate mofetil, and methylprednisolone. At 2 weeks post-transplant, the patient suffered acute rejection with urine production decreased to 200 cc/day and an increase in serum creatinine $>25\%$ (2.33 mg/dL to 5.23 mg/dL). The patient improved after five days of treatment with 250 mg methylprednisolone (iv) twice daily for 3 days, 720 mg mycophenolic acid twice daily, and 2 mg tacrolimus twice daily. On December 30, 2020, the patient had no complaints, urine output was 2500–3000 CC/24 hours, serum creatinine was 1.64, and blood tacrolimus level was 8.50 ng/mL, with maintenance therapy of 2 mg tacrolimus twice daily, 720 mg mycophenolic acid twice daily, and 16 mg methylprednisolone twice daily.

The patient had comorbid hypertension, congestive

heart failure, and obesity grade 1. Before the kidney transplant, a chest X-ray (CXR) was normal. At 12 months post-transplant, there were wounds on both legs of the patient who had difficulty healing. Debridement was performed, and the sensitivity culture of the wound beds showed bacteria on the right leg, which improved with antibiotics. However, the wound on the left leg did not heal and worsened. Then a skin biopsy identified the form of granulomatous inflammation typical of skin TB. The patient experienced significant weight loss (94 kg to 67.5 kg). The post-transplantation CXR results showed multiple nodules in the right lung with a negative smear sputum examination. The patient started receiving treatment for TB with a regimen of 300 mg isoniazid (INH), 600 mg rifampicin, 1,500 mg pyrazinamide, and 750 mg ethambutol. The patient was on tacrolimus 2 mg/d (1 mg-0 mg-1 mg), mycophenolic acid 720 mg two times a day, and methylprednisolone 4 mg/d.

Three months after receiving anti-tuberculosis therapy (ATT), the leg wound was better, however, there was a drastic decrease in the level of tacrolimus within the blood. There was also an enormous increase in serum creatinine after the immunosuppressant dose increased (Table 1). Ultrasound results on the kidney showed parenchymal inflammation of the allograft kidney transplant. Anti-TB therapy was also adjusted, namely rifampicin from 600 mg daily to 450 mg daily, and 750 mg levofloxacin once daily was added. However, the patient experienced allograft kidney failure and underwent hemodialysis after 4 months of anti-TB therapy. Unfortunately, during his treatment with hemodialysis, he accidentally passed away caused by an unknown cause of death.

Case II

A 30-year-old, Javanese female, suffered from chronic kidney disease due to hypertension since 2013 and had been undergoing hemodialysis for 7 years. The patient underwent a kidney transplant in July 2020 from an unrelated living donor with HLA matching 1/16 (HLA-C*07:02), negative virtual crossmatch and negative CDC crossmatching. The patient was diagnosed with hyperparathyroidism 2 years earlier and underwent parathyroidectomy surgery five months before transplantation, with the result of the biopsy being chief cell hyperplasia. Post-implantation, the patient experienced delayed graft function (DGF), characterized by decreased urine production, increased blood urea nitrogen (BUN) and serum creatinine, and required dialysis 3 times starting on day 8 post-implantation. The patient also received therapeutic plasma exchange therapy and continued with 7500 mg intravenous immunoglobulin on the 9th and 10th post-transplantation days. After the third hemodialysis session, the patient's condition improved, and she did not receive hemodialysis again. The patient's inorganic phosphate level was always high before the surgery. High levels of inorganic

phosphate caused by hyperparathyroidism are considered a risk factor for DGF. The patient's parathyroid hormone level was high at baseline before the surgery but decreased after parathyroidectomy. Parathyroid hormone levels rose again up to one year after surgery. Maintenance therapy was continued one year after transplantation, namely 3 mg tacrolimus daily (2 mg-0-1 mg), 360 mg mycophenolic acid twice daily, and 4 mg methylprednisolone once daily.

One-year post-transplantation (July 2021), the patient complained of cough with phlegm, shortness of breath, fever, and weight loss. GeneXpert sputum examination was found positive (MTB detected medium; rifampicin resistance not detected). The results of the CXR showed a picture of bronchitis. Any previous history of TB was denied, and the pre-transplant CXR results were within normal limits. She started receiving anti-TB therapy with a regimen of 300 mg INH once daily, 600 mg rifampicin once daily, 1500 mg pyrazinamide once daily, and 400 mg moxifloxacin once daily. There was a drastic increase in serum uric acid levels (4 to 10.4) a month post-ATT, therefore pyrazinamide was discontinued.

At three months after ATT, there was a drastic decrease in blood levels of tacrolimus, but the creatinine results remained good (Table 1). Then the tacrolimus dose was titrated from 4 mg to 8mg daily (4 mg-0-4 mg). Anti-TB therapy was also adjusted and the dose of rifampicin was reduced to 300 mg/d, while INH was increased to 400 mg/d, and moxifloxacin remained at 400 mg/d. She completed 9 months of ATT, and the renal allograft function was still stable, and still alive (full recovery).

Case III

A 29-year-old, Javanese male, suffered from chronic kidney disease for 1 year presumed to be due to unknown causes. The patient underwent routine hemodialysis 2 times a week for 7 years. The patient suffers from hypertension after undergoing hemodialysis. Based on the echocardiography result, the patient was diagnosed with hypertensive heart disease (HHD) and given candesartan, nifedipine, and isosorbide dinitrate. The patient was positive for anti-CMV IgG (latent CMV). He underwent kidney transplant therapy in May 2022 from an unrelated living donor with HLA matching 3/16 (HLA A*11:01; HLA DQB1*03:01; HLA DPA1*02:07), positive virtual crossmatching, and negative CDC crossmatching. He received induction with 125 mg methylprednisolone (iv), 720 mg mycophenolic acid tablet, 0.06 mg/kg weight tacrolimus, and 20 mg basiliximab. The maintenance therapy given was tacrolimus 4 mg/d (2-0-2), mycophenolic acid 360 mg/12 hours, and prednisone 5 mg/24 hours. The patient did not experience acute rejection. After kidney transplantation, kidney function gradually improved, and 1 month after the transplant the patient had no complaints with serum creatinine levels decreasing >20% (5.06 mg/dL to 1.2 mg/dL), BUN levels decreasing >20% (85.3 mg/dL to 16.7 mg/dL), and a blood tacrolimus level of 4.66

ng/ml. After the kidney transplant, he had retinopathy in both eyes. Treatment was 0.5% timolol maleate eye drops. He also complained of hair loss, and after the assessment, He was diagnosed with telogen effusion caused by chronic disease and he was given 2% regroup therapy.

Before the kidney transplant, the patient had a history of active pulmonary TB. The patient received anti-TB therapy for 1 year and he was declared cured. He had a negative smear of sputum, a negative GeneXpert, and the interferon-gamma release assays (IGRAs) test was positive but the patient had no symptoms. After the kidney transplant, the patient was given prophylaxis for TB such as 300 mg INH once daily, but six months later, the patient complained of a cough with phlegm, shortness of breath, and fever. There was a positive IGRA test and a CXR showed bilateral old active pulmonary TB. The patient started anti-TB therapy with a regimen of 400 mg INH once daily, 400 mg moxifloxacin once daily, and 225 mg rifampicin once daily. Three months after ATT, there was a drastic decrease in tacrolimus levels (7.75 ng/mL to 2.65 ng/mL), but creatinine levels remained stable (1.3 mg/dL to 1.07 mg/dL). Then, the tacrolimus dose was titrated from 4 mg/d (2-0-2) to 5 mg/d (3-0-2). Currently, the patient is still on ATT treatment (7th month) with a change in the ATT regimen such as 400 mg INH once daily and 400 mg moxifloxacin once daily. The condition of the renal allograft function is stable and ATT therapy is still ongoing.

Case IV

A 60-year-old, Javanese male, suffered from chronic kidney disease with comorbid hypertension and pulmonary hypertension. The patient had been routinely undergoing hemodialysis 2 times a week for 1 year. The patient underwent kidney transplantation therapy in December 2022 from an unrelated living donor with HLA matching 4/16 (HLA A*11:01, HLA DRB1*07:01, HLA DQA1*02:01, HLA DQB1*02:02, and HLA DPA1*02:01), negative virtual crossmatch, and negative CDC crossmatching. He received induction with 125 mg methylprednisolone (iv), 720 mg mycophenolic acid tablet, 0.06 mg/kg weight tacrolimus, and 20 mg basiliximab. The maintenance therapy given was tacrolimus 3 mg/d (0.5-0-1), mycophenolic acid 360 mg/12 hours, and methylprednisolone 4 mg/24 hours. The laboratory results before the kidney transplant showed that he had positive for IgG anti-CMV (latent CMV) and IgG anti-HSV1 (latent HSV) without any symptoms. No specific treatment was given to the patient and the patient was still approved for kidney transplantation.

A week after the kidney transplant, the patient's blood sugar result was 236 mg/dL (reference value 82-115 mg/dL). It is known that the patient has no history of high blood sugar and there are no classic and nonclassical complaints of diabetes mellitus (DM). There was no history of consumption of sugar medication. Every month

Table 1. Post-transplant patient characteristics and outcomes

Characteristic or Outcome	Patient 1	Patient 2	Patient 3	Patient 4
BMI (kg/m ²) 1-year post-transplant	22.5	21.16	18.76	19,24
Post-transplant INH prophylaxis	No	No	No	No
Immunosuppressive agent	Tacrolimus, MMF	Tacrolimus, MMF	Tacrolimus, MPA	Tacrolimus, MPA
Corticosteroids	Yes	Yes	Yes	Yes
Acute rejection	Yes	No	No	No
Delayed graft function	No	Yes	No	No
Clinical features	Cellulitis, unhealing leg wound, weight loss	Cough, shortness of breath, fever	Cough, shortness of breath, fever	Pleuritic chest pain
TB site	Disseminated	Pulmonary	Pulmonary	Pleura
Diagnosed tool of positive TB	Skin biopsy, CXR	Sputum GeneXpert	IGRA test, CXR	IGRA test, MSCT-scan thorax
Time to diagnosis of post-transplant TB (mo)	12	12	6	2
Time to the most decline tacrolimus trough post-ATT (mo)	3	3	3	3
Tacrolimus trough (ng/mL)				
At diagnosed TB	6.6	5.00	7.75	12.5
3rd mo after ATT	2.1	1.8	2.38	10.1
6 th mo after ATT	No data	4.00	4.33	No data
Serum creatinine level (mg/dL)				
At diagnosed TB	1.44	1.14	1.3	0.99
3rd mo after ATT	6.75 →12.3 (HD)	2.9	0.96	0.98
6 th mo after ATT	No data	1.12	1.15	No data
ATT regimen	300 mg INH, 600 mg rifampicin, 1500 mg pyrazinamide, and 750 mg ethambutol	300 mg INH, 600 mg rifampicin, 1500 mg pyrazinamide, and 400 mg moxifloxacin	400 mg INH, 400 mg moxifloxacin, and 225 mg rifampicin	300 mg INH, 400 mg ethambutol, 500 mg pyrazinamide, and 400 mg moxifloxacin
ATT drug adjustment (maintenance)	450 mg rifampicin, add 750 mg levofloxacin, INH, pyrazinamide, and ethambutol, the same dose	300 mg rifampicin, 400 mg INH, and the same moxifloxacin dose	The same dose of INH and moxifloxacin	INH and moxifloxacin same dose, 25 mg pyridoxine
Immunosuppressant drug adjustment	At 1 st mo after ATT: tacrolimus 2 mg/d to 3 mg/d, mycophenolic acid 360 mg q12h to 720 mg q12h, methylprednisolone 4 mg/d to 32 mg/d	At 3 rd mo after ATT: tacrolimus 4 mg/d to 8 mg/d, mycophenolic acid 360 mg, methylprednisolone 4 mg/d	At 1 st mo after ATT: tacrolimus 4 mg/d to 5 mg/d, mycophenolic acid 360 mg, methylprednisolone 4 mg/d	At 1 st mo after ATT: tacrolimus 1.5 mg/d to 3 mg/d, mycophenolic acid 360 mg, methylprednisolone 4 mg/d
Adverse drug reaction	None	Hyperuricemia	None	None
Allograft outcome	Allograft failure	Stable renal allograft function	Stable renal allograft function	Stable renal allograft function
Clinical outcome	Death	Full recovery	on ATT therapy	on ATT therapy

ATT, Antituberculosis therapy; BMI, Body mass index; CXR, Chest X-ray; IGRA, Interferon-gamma release assay; INH, Isoniazid; MMF, Mycophenolate mofetil; MPA, Mycophenolate acid; MSCT, Multiscale computed tomography; TB, Tuberculosis.

after the transplant, the patient's blood sugar was always above 180 mg/dL and it was included in the New Onset DM After Transplant (NODAT) condition. The therapy given was insulin until now.

The patient did not have a history of TB or a history of contact with TB patients. Before the kidney transplant, the patient had a negative IGRA test, and CXRs showed no abnormalities. Two months after the kidney transplant, the patient complained of persistent pleuritic chest pain. A CXR showed no abnormalities, but after a multiscale computed tomography (MSCT) scan of the chest, a solid mass was found in the pleura of the left hemithorax on the posteroinferior aspect, accompanied by multiple pleural nodules suspected of mesothelioma, pulmonary ground glass nodules in the apical segment of the right superior lobe of the right lung, and pleural thickening in the apical segment hemithorax. The patient had a positive IGRA test post-transplant. The patient was diagnosed with pleural TB with the treatment given 300 mg INH once daily, 1000 mg ethambutol once daily, 1250 mg pyrazinamide once daily, and 400 mg moxifloxacin once daily. Three months after ATT, there was a drastic decrease in tacrolimus levels (12.5 ng/mL to 8.82 ng/mL) but creatinine levels remained stable (0.99 mg/dL to 0.9 mg/dL). Then, the tacrolimus dose was titrated from 1.5 mg/d (0.5-0-1) to 3 mg/d (2-0-1). Currently, the patient is still on ATT treatment (month 5) with changes to the ATT regimen, such as 300 mg INH once daily, 400 mg moxifloxacin once daily, and 25 mg vitamin B6 (pyridoxine) once daily. The condition of the renal allograft function is stable and ATT therapy is still ongoing.

Discussion

There exists a direct correlation between the total epidemiological risk of environmental circumstances and the incidence of TB infection among transplant recipients (5). Indonesia is the second highest TB-incidence country,

according to WHO estimates. The incidence rate of TB in 2021 is 354 per 100 000 people. The incidence of TB in recipients is not acknowledged with certainty, however, with the high incidence of TB within the community, it is likely to be just as high. Post-transplant TB entails the respiration system (50%), disseminated involvement (30%), lymph nodes (5%), integumental and soft tissues (4%), genitourinary system (4%), intestines (3%), the central nervous system (2%), bone (1%), and fever of unknown origin (16%) (5). Around 85% of TB cases were lung involvement, and 15% of TB cases were extrapulmonary. However, under the immunocompromised condition, extrapulmonary TB might be bigger than pulmonary TB. In this case, two cases of TB involved the lungs, one case was disseminated (TB of the lungs and skin), while the other case was extrapulmonary (TB pleura) (6).

Solid organ transplant recipients have a TB infection mortality rate of up to 30%, which is 20-74 times greater than in the preferred population. Factors such as disseminated disease, previous acute rejection, anti-T-cell antibody therapy, graft rejection, steroid treatment, and concomitant opportunistic infections contribute to higher mortality (4,7,8). This case series demonstrated graft failure in 50% of cases. Patients who experience allograft kidney failure are those with a disseminated TB disease, these patients have a history of previous acute rejection and have received anti-T cell antibody therapy. The fourth patient in this case series received immunosuppressant therapy and took steroids. However, one patient died and three patients were alive in our case series. The baseline characteristics of the four cases in this series are presented in Table 2.

According to a cohort study, from 1 to 168 months after transplantation, the incidence of post-transplant TB changed to 2.1% on average, with 11.8% of patients having disseminated TB (9). In accordance with the study, TB following kidney transplantation is linked to an increased

Table 2. Baseline characteristics of the patients

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	42	31	29	60
Gender	Male	Female	Male	Male
BMI (kg/m ²) pre-transplant	31.4	18.11	20.94	19.72
Prior TB exposure	No	No	Yes	No
PPD/IGRA test	No data	Notes	Positive	Positive
Pre-transplant CXR	Normal	Normal	Old active pulmonary duplex TB	Normal
Cause ESRD	Hypertension	Hypertension	Unknown	Hypertension and pulmonary Hypertension
Other Comorbidities	CHF; obesity grade 1	Tertiary hyperthyroidism	HHD; Latent CMV	Latent CMV and HSV1
Pre-transplant INH prophylaxis	No	No	Yes	Yes
Living donor-related	Unrelated	Unrelated	Unrelated	Unrelated
HLA match	2/16	1/16	3/16	4/16

BMI, Body mass index; CHF, Congestive heart failure; CMV, Cytomegalovirus; CXR, Chest X-ray; ESRD, End-stage renal disease; HLA, Human leukocyte antigen; HSV, Herpes simplex virus; IGRA, Interferon-gamma release assay; INH, Isoniazid; PPD, Purified protein derivative; TB, Tuberculosis.

risk of allograft renal failure and severe acute kidney injury, as well as with the interaction of ATT treatment with immunosuppressants, depending on the drug regimen used. That study observed a reduction in graft survival, disseminated TB disease occurred in 38.8% of mortality, and allograft losses (10). These findings are consistent with our case reports in which only one patient with disseminated TB ultimately developed allograft kidney failure compared to the other patient with pulmonary TB. These findings demonstrate that prevention and early diagnosis of TB in kidney transplant recipients are essential.

In half of the cases, the recipient acquired TB infection 1 year after kidney transplantation (Table 1). This pattern is in line with another study that discovered that during the first year following their transplantation, almost half of the patients of kidney transplants acquired TB. In the first year following their transplant, more than 50% of kidney transplant recipients have TB (4). Although opportunistic infections such as TB could occur 1-6 months after transplantation and beyond 6 months the degree of immune suppression for most patients decreases (11). The other half of our recipients acquired TB infection 2 months and 6 months after kidney transplantation. Because of this, TB should be regarded as a potential cause for patients with fever of unknown origin (12).

TB develops earlier in those who have had previous exposure to TB. The cell response to TB-specific antigens (positive TST or IGRA) or the aftereffects of granulomatous infection in CXRs can serve as indicators of prior TB infection (4). In our patients, except for the third patient, there was no previous history of TB from CXR, and data from the IGRA test was negative in the fourth patient. Meanwhile, in the third patient, a past TB diagnosis was evident from the CXR and a positive result of the IGRA test. The third patient had a previous TB infection, one of the reasons for the reactivation of TB infection after kidney transplantation. The reactivation of a prior infection is the most frequent cause of post-transplant TB. Furthermore, there are several other predisposing factors, one of which is immunosuppressive drugs, that exist in all cases (4).

The diverse and uncommon clinical presentations of TB in kidney transplant patients frequently result in delayed diagnosis and unfavorable consequences. Fever (more common) and 30%-50% of TB cases after transplantation are extrapulmonary or disseminated. The disseminated disease was described as the involvement of 2 or more non-adjacent organs with positive TB culture, without or with granulomas. A diffuse pulmonary infiltration has been shown in the CXR features of post-transplant TB, as opposed to cavitory lesions, which might be common in the general population (4,13). In our cases, fever was only found in 2 cases (50%), 1 case (25%) had symptoms of sores on the legs that did not heal, and 1 case (25%) had pleuritic chest pain. Disseminated TB was found in 2

cases (50%) such as skin TB with pulmonary TB features and pleural TB. In contrast, the other case was pulmonary TB (Table 1).

Close monitoring for ATT drug interactions with immunosuppressive drugs is used in kidney transplant recipients because that interaction can increase the risk of allograft rejection. Tacrolimus is a calcineurin inhibitor commonly used to prevent allograft transplant rejection. The immunosuppressant levels, especially the drug tacrolimus in the blood, need to be closely monitored under several conditions including the start of TB treatment, following the cessation of rifampicin or rifabutin, or following the dose modification of an immunosuppressant (5,14). Because of its potent MTB sterilizing effect, rifampicin is utilized in the treatment of TB. Strong CYP3A4 inducer Rifampicin also functions as a calcineurin inhibitor, mycophenolate mofetil, mTOR inhibitor, and corticosteroid (14). This can lead to acute rejection and, in a few cases, 30% graft rejection and 20% graft loss (5).

Rifabutin is a less effective cytochrome inducer than rifampicin. An alternate medication to rifampicin that has less interactions with tacrolimus is rifabutin. Rifabutin is not continually available, so another alternative that can be executed is to increase the dose of calcineurin inhibitors (tacrolimus) by as much as 3-5 times. Nevertheless, this entails increased expenses and a greater likelihood of potential consequences, such as nephrotoxicity. One study found that adding ketoconazole to tacrolimus increased serum tacrolimus tiers without lowering the efficacy of anti-TB drugs. Furthermore, in purpose to prevent major side effects, such as graft failure and anti-TB medication resistance, clinical adjustments to dosage and duration are essential throughout anti-TB treatment (12).

Isoniazid may elevate corticosteroid levels and their associated side effects, while streptomycin used alongside cyclosporine and sirolimus could lead to nephrotoxicity. Fluoroquinolones with corticosteroids may heighten the risk of tendon rupture, and corticosteroids can decrease INH levels (14). TB treatment is challenging due to toxicity and drug interactions, particularly between rifampicin and immunosuppressive therapy. INH and rifampicin are the preferred choices, but the duration of treatment varies. Rifampicin can lower immunosuppressant drug levels, so it can induce graft dysfunction and may not recommended as a first-line drug (3). Before transplantation, a 4-month period of treatment with rifampicin 10 mg/kg daily (maximum dose 600 mg/d) may be implemented. However, due to medication interactions with immunosuppressant medications, it should be avoided following transplantation. It is not advised to take pyrazinamide and rifampicin together every day for two months since transplant recipients have a significant risk of hepatotoxicity. Weekly INH combined with 12 weeks of rifampentine, administered under direct observation, is not suggested for immune-competent individuals who are

kidney transplant candidates (4).

In all cases, rifampicin was still used as anti-TB therapy but gave different effects: in the case of disseminated TB, allograft kidney failure occurred, but in the other cases of pulmonary and pleural TB, the kidney transplant function was still good after adjustment of the immunosuppressant dose, as well as the ATT. This difference indicates that other factors may influence the occurrence of allograft kidney failure. Close monitoring at the right time can reduce the incidence of allograft kidney failure.

These cases demonstrated that anti-TB drugs (especially rifampicin) could reduce tacrolimus levels and lead to graft failure if prompt intervention is not given. In this case, the outcome was contradictory in that in one case, graft failure occurred, and in the other case, it could be resolved. TB treatment with kidney allograft function is still good (stable). Therefore, further research is needed to examine the risk factors involved in allograft kidney failure in post-transplant TB recipients receiving ATT therapy and immunosuppressant drugs and examine the efficacy of this shorter-term treatment regimen. Clinicians must maintain a high clinical suspicion of post-transplant TB due to diagnostic challenges in order to start therapy early and lower morbidity and death (14,15).

The existence of immunosuppression status in kidney transplant, their morbidity of active TB is greater compared with general population. To prevent this condition, kidney transplant recipients should be given TB prophylaxis. Given the increased risk of liver damage following INH treatment, prophylactic INH administration may be helpful in lowering the risk of TB infection by monitoring the liver function. Many transplant centers do not use INH prophylaxis on a regular basis. Whereas, the American Thoracic Society suggested that INH should only be discontinued if liver enzyme levels rise three to five times higher than normal in symptomatic patients (15).

The need for TB preventive treatment in patients undergoing kidney transplants is also challenging. Is TPT needed in all patients before transplantation or only in patients with positive IGRA still needs to be addressed. Finally, public health efforts at both global and domestic levels are needed to minimize this disease.

Conclusion

Diagnosis and management of TB post kidney transplantation involves challenges, particularly since most patients show atypical symptoms and varied clinical outcomes. Tacrolimus and anti-TB drugs can interact in ways that compromise both the effectiveness of immunosuppressive treatments and the potency of anti-TB drugs. For this reason, during the first three months of ATT, frequent and close monitoring of drug adjustments is essential. Within a year following transplantation, TB prophylaxis is practically required for transplant recipients, particularly in countries with high TB prevalence rates. Systematic assessment to screen for TB infection and give

TB preventive therapy for those who are needed before transplantation is recommended, especially in endemic countries.

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Authors' contribution

Conceptualization: Siti Nur Rohmah.

Data curation: Siti Nur Rohmah and Alfreda Amelia Khotijah.

Formal analysis: Siti Nur Rohmah.

Funding acquisition: Siti Nur Rohmah.

Investigation: Siti Nur Rohmah, Metalia Puspitasari, Yulia Wardhani, and Nur Rahmi Ananda.

Methodology: Siti Nur Rohmah.

Project administration: Siti Nur Rohmah.

Resources: Siti Nur Rohmah.

Validation: Metalia Puspitasari, Yulia Wardhani, and Nur Rahmi Ananda.

Supervision: Metalia Puspitasari, Yulia Wardhani, and Nur Rahmi Ananda.

Visualization: Siti Nur Rohmah and Alfreda Amelia Khotijah.

Writing-original draft: Siti Nur Rohmah and Alfreda Amelia Khotijah.

Writing-review and editing: Siti Nur Rohmah, Alfreda Amelia Khotijah, Metalia Puspitasari, Yulia Wardhani, and Nur Rahmi Ananda.

Conflicts of interest

The authors declare no competing interest.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The consent was informed to all participants and parents or guardians. The authors have observed and adhered to the ethical issues or standards including avoiding plagiarism, data fabrication, and double publication.

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