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CASE REPORT

Tuberculosis in kidney transplant recipients: A case series

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Abstract

Solid organ transplant recipients have an elevated risk of tuberculosis (TB) with high mortality. Data about TB in this population in the United States is sparse. We present four cases of active tuberculosis in kidney transplant recipients at our center. All patients had possible TB exposure prior to transplant and all were diagnosed with active TB within the first year of transplant. Disseminated TB was seen in half of the patients with extra-pulmonary TB being more common affecting lymph nodes, pericardium, and the kidney allograft. Delay in diagnosis from onset of symptoms ranged from fifteen days to two months. Two patients died from TB. TB is a largely preventable and curable disease. However, challenges remain in the diagnosis due to most recipients presenting with atypical symptoms. Physicians should maintain a high degree of suspicion for TB to promptly diagnose and treat post-transplant thereby minimizing complications. A review of the literature including the epidemiology, pathogenesis, clinical presentation, diagnosis and treatment options are discussed.

Key words: Mycobacterium tuberculosis; Kidney transplant; Disseminated disease; Tuberculosis

Core tip: Tuberculosis is a largely preventable and curable disease that should be suspected in all solid organ transplant recipients who present with unexplained fevers, pulmonary or extra-pulmonary symptoms. This case report describes the varied presentations of tuberculosis in kidney transplant recipients and provides the most recent recommendations regarding diagnosis and treatment.

Anand M, Nayyar E, Concepcion B, Salani M, Schaefer H. Tuberculosis in kidney transplant recipients: A case series. *World J Transplant* 2017; 7(3): 213-221 Available from: URL: http://www.wjgnet.com/2220-3230/full/v7/i3/213.htm DOI: http://dx.doi.org/10.5500/wjt.v7.i3.213

INTRODUCTION

The overall incidence and prevalence of mycobacterium tuberculosis (TB) in solid organ transplant recipients is not well defined. The rates of TB in this population are mostly based on data available from individual study cohorts reported in the literature. In the western world, TB is a rare opportunistic infection with significant morbidity and mortality. Clinical presentation in immunocompromised individuals, including transplant recipients is often atypical and diverse. This leads to delay in the diagnosis and advanced disease at the time of diagnosis. In addition, inadequate host response in this setting poses a treatment challenge. The higher toxicity of treatment and concurrent use of immunosuppressive medications with drug interactions further generate complexity in management. We describe four cases of active TB in our kidney transplant recipients and explore the epidemiology, clinical presentation, management and outcomes of TB disease in this population.

CASE REPORT

Case 1

A 63-year-old Vietnamese male with end stage renal disease due to IgA nephropathy received an expanded criteria deceased donor kidney transplant (DDKT) in 2012 (5 antigen mismatch, 5% panel reactive antibody, PRA). He received induction with alemtuzumab and solumedrol and was maintained on tacrolimus and mycophenolate mofetil. There were no surgical complications or episodes of acute rejection in the post-transplant period. Allograft function stabilized with a serum creatinine (Cr) of 1.8 mg/dL. His past medical history was notable for incarceration in Vietnam, prior hepatitis B exposure with protective anti-Hepatitis B surface antibody, positive tuberculin skin test (TST) and a non-calcified nodule on chest X-ray (CXR). He had been in the United States for twenty years prior to his transplant. He did not receive isoniazid (INH) prophylaxis before undergoing kidney transplant. At one-year post-transplant, he was admitted with fever, palpitations and 3 cm non-tender submental lymph node. Labs were notable for acute kidney injury (AKI) with Cr of 3 mg/dL and urinary retention that resolved with urinary catheter placement and treatment for an enlarged prostate. CXR revealed bilateral pleural effusions and a large pericardial effusion. Fine needle aspiration of the lymph node and pericardial fluid grew Mycobacterium tuberculosis (MTB). He received anti-tubercular therapy (ATT) with 2 mo of Rifampin, INH, Pyrazinamide and Ethambutol (RIPE) and 4.5 mo of INH and Rifampin (IR). His treatment course was complicated by transaminitis with reactivation of hepatitis B leading to end stage liver disease. He was treated with tenofovir with resolution of transaminitis. Patient completed 6.5 mo of ATT and has been cured of TB. His kidney transplant failed three years later due to BK nephropathy, and he was initiated on hemodialysis.

Case 2

A 67-year-old Caucasian male, Vietnam War veteran with ESRD presumed secondary to hypertension received a DDKT in 2013 (0 antigen mismatch, PRA 36%). He received induction with alemtuzumab and solumedrol and was maintained on tacrolimus, mycophenolate mofetil, and prednisone. Pre-transplant CXR showed prior granulomatous disease. He was not tested for latent TB infection (LTBI). Two months after transplant, he was admitted with fever and progressive shortness of breath. CXR revealed a miliary pattern of infiltrates. He developed acute respiratory failure and septic shock requiring intubation and multiple vasopressors. The day after admission, sputum samples returned positive for acid-fast bacilli (AFB), and later grew MTB. Clinical course was complicated by development of presumed macrophage activation syndrome (MAS). He received neupogen for pancytopenia but bone marrow biopsy could not be obtained due to agitation. He did not receive intravenous steroids or chemotherapy for MAS. Patient died within three days of admission.

Case 3

A 38-year-old Indonesian woman living in United States for ten years with ESRD due to IgA nephropathy on hemodialysis for 10 years received a DDKT in 2015 (6 antigen mismatch, PRA 0%). She received induction with alemtuzumab and solumedrol and was maintained on tacrolimus, mycophenolate mofetil, and prednisone. There were no surgical complications or episodes of acute rejection in the post-transplant period. Allograft function was excellent with serum Cr of 1.0 mg/dL. Pre-transplant work up was notable for positive TST with normal CXR. She was started on INH immediately after transplant and received nine months of therapy for LTBI. One month after completing INH therapy, she was admitted with persistent fevers, night sweats and acute kidney injury, serum Cr of 2 mg/dL. Fever work up showed adenovirus in the blood and urine. There was increased flurodeoxyglucose uptake in the kidney allograft on positron emission tomography scan. Biopsy of the kidney transplant showed necrotizing granulomatous interstitial nephritis. Differential diagnosis of the granulomatous interstitial nephritis included renal transplant TB and adenovirus infection. Renal pathology changes were not consistent with adenovirus infection. AFB smear and cultures were negative in the urine and renal biopsy specimens. Due to persistent fevers, worsening renal function and clinical suspicion for TB, she was started on RIPE and Moxifloxacin. Moxifloxacin was added as a fifth agent due to concern for INH resistance given she was treated with INH monotherapy for LTBI. Fevers, night sweats and AKI resolved on treatment without addition of cidofovir, which supported the diagnosis of renal transplant TB. Her IS was modified with discontinuation of MMF. She is currently maintained on tacrolimus and prednisone. She completed 6 mo of ATT and is cured of TB. Renal allograft function is stable

with Cr of 1.3 mg/dL.

Case 4

A 67-year-old Caucasian male with ESRD, secondary to diabetes mellitus on hemodialysis for 2 years received a DDKT in 2015 (4 antigen mismatch, PRA 0%, A2 to B kidney). He received induction with alemtuzumab and solumedrol and was maintained on tacrolimus, mycophenolate mofetil, and prednisone. His pre-transplant CXR showed calcified lung nodules, and he had a negative interferon gamma release assay (quantiferon gold). He presented two and a half months' post-transplant with two weeks of intermittent fever, malaise, progressive dyspnea and lower extremity swelling. He was diagnosed with bilateral lower extremity deep vein thrombus and pulmonary embolism for which anticoagulation was initiated. Due to intermittent fevers, computed tomography (CT) of the chest was done that showed a few scattered sub centimeter non-calcified pulmonary nodules and a 2 cm right paratracheal lymph node concerning for granulomatous disease. Fungal testing including serum galactomannan, serum cryptococcal antigen, beta-D-glucan levels and urine histoplasma antigen, was negative. Bronchoscopy was performed with AFB stain positive in the bronchoalveolar lavage (BAL). AFB and non-necrotizing granulomas were seen on trans-bronchial lung biopsy. MTB complex polymerase chain reaction (PCR) was positive in both the BAL and blood, and cultures from both grew MTB. Sputum cultures later grew pan susceptible MTB. He was discharged on a four-drug regimen with RIPE. Two weeks later, he was readmitted with recurrence of fever, altered mental status and partial loss of vision. Repeat CT of the chest showed worsening bilateral pulmonary infiltrates.

Moxifloxacin was added to his regimen. ATT drug levels were obtained and found to be therapeutic. Sputum, urine and blood cultures returned negative for AFB. Neurology work up including magnetic resonance imaging of the brain and lumbar puncture was negative. Patient developed AKI with serum Cr of 3 mg/dL. Ethambutol dose was decreased from 1600 mg daily to 1600 mg every 36 h and pyrazinamide dose was lowered from 2000 mg daily to 2000 mg thrice weekly. Ethambutol was subsequently discontinued due to worsening visual changes and amikacin was added to the treatment regimen of isoniazid, rifampin, pyrazinamide and moxifloxacin. His IS was ultimately tapered to prednisone alone due to worsening of TB with persistent fever and progressive pulmonary infiltrates. Renal allograft function continued to decline likely due to tapering off IS and aminoglycoside toxicity ultimately leading to allograft failure. He was started on hemodialysis 4 mo after initiation of ATT and died three months later.

DISCUSSION

Epidemiology

Even before MTB was discovered, Laennec described the diseased lung cavities on autopsies. Historically this was referred to as "consumption" owing to significant weight loss and finally death that consumed patients. In 1839, Johann Schonle coined the term tuberculosis from the Latin word "tuberculum" which means small pimple or a bump. The bacillus was identified by Robert Koch as Mycobacterium tuberculosis on March 24, 1882 which is commemorated as World TB day.

The global TB incidence and prevalence has been declining per the most recent WHO Global TB report[1]. The incidence of TB globally is 18% lower in 2014 as compared to 2000 and TB prevalence is 42% lower as compared to 1990. TB mortality has also fallen 47% since 1990. The incidence rate is highest in South East Asia and the Western Pacific and lowest in Western Europe, Canada, United States, Australia and New Zealand. The CDC Morbidity and Mortality Report in early 2016 shows leveling of TB incidence in the United States at 3 cases/100000 persons in 2013-2015, after two decades of annual decline[2]. Approximately 70% of the cases are in foreign-born individuals, with Mexico, the Philippines, India, Vietnam and China accounting for the top five countries of origin. In our case series, two out of four were from Southeast Asia which is considered to be endemic for TB. Among those born in the United States, native Hawaiians/other Pacific Islanders have the highest incidence followed by American Indians and Alaskan Natives. Almost half of all reported TB cases in the United States are reported from California, Florida, New York and Texas. The TB incidence in foreign born individuals has been steadily declining compared to stabilization of TB incidence among those born in the United States, pointing to TB transmission in the United States. This has been confirmed by molecular genotyping. Risk factors for TB outbreaks include substance abuse, incarceration and homelessness.

Data regarding the prevalence and incidence of TB in solid organ transplant recipients is sparse. Prevalence of active TB is estimated to be 1.2%-6.4% in developed countries and up to 15% in highly endemic areas[3]. A study in 1998 estimated a 0.35%-1.2% incidence in renal transplant recipients in the United States[4]. Risk in solid organ transplant recipients is estimated to be 20-74 times higher than the general population with a high mortality rate of up to 30%. Mortality of TB is higher in patients with disseminated disease, prior rejection and those who received anti-T cell antibody therapy[4]. Another study found higher mortality with graft rejection, steroid treatment and concomitant other opportunistic infection[3]. Diabetes mellitus and chronic liver disease have also been associated with greater mortality[5]. Our case series show a mortality of 50%. Half of our TB cases had disseminated disease. All four patients received anti-T cell antibody therapy and three were on steroids. Half of our patients had diabetes mellitus. Baseline characteristics of our patients are listed in Table 1.

Over 50% of renal transplant recipients develop TB within the first year of transplant[4]. TB develops earlier

Table 1 Baseline characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yr)	63	67	38	67
Ethnicity	Vietnamese	Caucasian	Indonesia	Caucasian
Sex	Male	Male	Female	Male
BMI (kg/m^2)	32	33	21	32
Prior TB exposure	Incarceration in Vietnam	Vietnam war veteran	Lived in Indonesia till age 25	None
PPD/IGRA	Positive	Not done	Positive	Negative
Pre-transplant CXR	Non-calcified lymph nodes	Prior granulomatous disease	Normal	Calcified lung nodules
Smoking	Yes	No	No	No
Diabetes mellitus	Yes	No	No	Yes
Hepatitis C	No	No	No	No
Chronic liver disease	Prior hepatitis B exposure	No	No	No
Pre-transplant INH prophylaxis	No	No	No	No

BMI: Body mass index; TB: Tuberculosis; PPD: Purified protein derivative; IGRA: Interferon gamma release assay; CXR: Chest X-ray; INH: Isoniazid.

in those with prior TB exposure[3]. Markers for prior infection include cellular response to TB specific antigens (positive TST or interferon gamma release assay, IGRA) or sequelae of granulomatous infection on CXR. Older patients are more likely to have reactivation following transplantation than younger patients, particularly in the developed world. All of our cases had prior TB exposure and developed TB early after transplant, half developed disease within the first 3 mo following transplant.

Factors predisposing to TB both in the general population and transplant recipient include country of origin, history of untreated latent TB infection, cigarette smoking, body mass index < 18.5, diabetes mellitus, chronic kidney disease, chronic liver disease, lupus, human immunodeficiency virus, silicosis, gastrectomy, jejuno-ileal bypass, as well as social risk factors (homelessness, incarceration, alcoholism and known TB contact)[6,7]. The main predisposing factor in our center's experience was residence from or previous travel to an endemic region (Table 2).

Pathogenesis

TB is usually acquired *via* inhalation of bacilli into the lungs. Progression to clinical disease depends on the infecting dose and virulence of the Mycobacteria as well as the development of host cell mediated immunity. The most common reason for post-transplant TB is reactivation of previous infection. In patients with prior exposure, the risk is generally inversely related to the time from acquisition to transplantation. Rarely, TB can be donor-derived and transmitted through the transplanted organ. TB can be acquired post-transplant, more commonly in TB endemic countries, or nosocomial as part of outbreaks in renal transplant units[8].

Clinical presentation

The clinical presentation of TB in transplant recipients differs from the general population in that symptoms are more unusual and varied, often leading to a delay in diagnosis and poor outcomes. Fever is seen more commonly, and approximately 30%-50% of TB after transplant is extra-pulmonary or disseminated[4,7]. Disseminated disease is defined as involvement of two or more non-contiguous organs with positive TB cultures, with or without granulomas[4].

CXR's in post-transplant TB show diffuse pulmonary infiltrates rather than cavitary lesions which are more commonly seen in the general population[7]. In our case series, fever was present in all four patients. Cervical lymphadenopathy was seen in one patient. Disseminated TB was seen in two of the four patients with extra-pulmonary involvement of lymph nodes, pericardium and the renal allograft. Two patients had pulmonary TB and one of them had disseminated disease. Only one presented with cough. Patients with pulmonary involvement showed military pattern and bilateral diffuse pulmonary nodules on CXR.

Diagnosis and pre-transplant screening

Diagnosis of latent TB is an indirect measure of possible infection by detection of a cellular response to MTB specific antigens in the absence of symptoms. The two types of tests are *in-vivo*: Tuberculin skin test (TST) done by intradermal injection of purified protein derivative (PPD); and *ex-vivo*: IGRA (Quantiferon gold test or T-spot TB test). PPD is a glycerol extract of the tubercle bacillus and is not species specific. Induration of 5 mm or more is considered to be positive in transplant candidates. If the first test is negative, a follow-up second test is recommended two weeks later. This leads to a "booster effect" due to amnestic recall of immunity and can identify an additional 10% of cases[9]. Limitations of PPD testing include a higher rate of false negatives in the immunocompromised host, confounding by non-tubercular mycobacteria and prior BCG vaccination, and need for trained staff and a second visit for interpretation of the test by a qualified provider. IGRA utilizes sensitized T cells that release interferon-gamma. The advantages of IGRA over PPD include improved specificity due to MTB specific antigens that do not cross-react with BCG and the use of positive and negative controls that may differentiate true negatives from those that result from anergy or overt immunosuppression[10]. Performance of IGRA is better in low prevalence countries as compared to endemic

Table 2 Post-transplant patient characteristics and outcomes

	Patient 1	Patient 2	Patient 3	Patient 4
INH prophylaxis	No	No	Yes	No
T cell depleting antibody	Yes	Yes	Yes	Yes
Immunosuppressive	Tacrolimus, MMF	Tacrolimus, MMF	Tacrolimus, MMF	Tacrolimus, MMF
Corticosteroid	No	Yes	Yes	Yes
Acute rejection (6 mo prior to TB diagnosis)	No	No	No	No
Clinical features	Fever, palpitations, cervical LN	Fever, shortness of breath, cough	Fever, acute kidney injury	Fever, shortness of breath, leg swelling
TB site	Disseminated	Pulmonary	Extra-pulmonary	Disseminated
Time to symptom onset (mo)	11.5	2	9	2
Time to diagnosis, post-transplant (mo)	12	3	11	3
Treatment regimen	RIPE	None	RIPE-M	RIPE-M, Amikacin
Treatment duration (mo)	6.5	N/A	6	7
Adverse drug reaction	Hepatotoxicity	N/A	None	Neurologica,vision loss
Other complication	HBV reactivation, acute liver injury	Septic shock, MAS	None	VTE, IRIS, allograft failure
Outcome	Cured	Death	Cured	Death

INH: Isoniazid; MMF: Mycophenolate mofetil; TB: Tuberculosis; LN: Lymphadenopathy; RIPE: Rifampin, isoniazid, pyrazinamide, ethambutol; RIPE-M: Rifampin, isoniazid, pyrazinamide, ethambutol, moxifloxacin; HBV: Hepatitis B virus; MAS: Macrophage activation syndrome; VTE: Venous thromboembolism; IRIS: Immune reconstitution inflammatory syndrome.

areas[11]. Both these tests cannot differentiate between latent TB and active TB. ESRD and immunosuppressant use are responsible for a higher rate of false negative or equivocal results of immune based T-cell assays. Uremia is associated with impaired co-stimulatory function of the antigen-specific T-cells leading to a defect in T-cell function. One of our transplant recipients had a negative IGRA in the presence of calcified nodules on chest imaging.

Immunosuppressants such as T-cell depleting antibodies, corticosteroids and calcineurin inhibitors cause a reduction in the number of T-cells, affect their interaction with antigen-presenting cells and impair cytokine induction[12].

Diagnosis of TB in transplant recipients is often delayed. In our case series, delay in diagnosis from onset of symptoms ranged between fifteen days and two months. Diagnosis of active TB is made by demonstration of AFB on smear microscopy and isolation of mycobacteria in culture of the body fluid. AFB blood cultures should be done if there is a suspicion for disseminated TB. For pulmonary TB, three samples of sputum are sent 8-24 h apart with at least one being an early morning sample. Sputum induction with aerosolized hypertonic saline can be employed for patients who are unable to expectorate. Invasive diagnostic tests such as bronchoscopy with bronchoalveolar lavage may be necessary for diagnosis. Sensitivity and specificity of sputum AFB smear microscopy is 45%-80% and 50%-80%, respectively[13].

Sensitivity and specificity of sputum culture is 80% and 98%, respectively[14,15]. Cultures need to be incubated for 6-8 wk to isolate MTB. Drug susceptibility testing should be done on all positive MTB cultures. Nucleic acid amplification (NAA) assays are available for rapid diagnosis of TB. These tests can be done from cultures or direct tissue samples. The Centers for Disease Control (CDC) recommends sending the first sputum sample for NAA testing. These assays can detect target specific MTB complex RNA/DNA sequences with nucleic acid probes in 24-48 h. Xpert MTB/Rif test is an automated NAA test that detects rifampin resistance simultaneously in two hours. Rifampin resistance is a marker of multi-drug resistant (MDR) TB. Sensitivity and specificity of NAA tests in AFB smear positive respiratory secretions is over 95% and is not affected by non-tuberculous *Mycobacteria* (NTM) or immunosuppression. They have lower sensitivity, 75%-85% in smear negative sputum[16-18]. These tests should be performed within the first few days of ATT and a negative NAA test does not exclude TB. Cultures are still required for species identification and for drug susceptibility testing. NAA assays do not perform as well for other clinical specimens and the overall evidence regarding their use in transplant patients is lacking at this time. Tissue biopsy of the involved organ and/or fluid for histopathology evaluation, AFB smear and culture should be obtained in suspected extra-pulmonary TB.

In our case series, we diagnosed TB disease if any of the following criteria were met: (1) isolation of MTB in culture of sputum, blood or any body fluid, with or without detection of AFB on smear; (2) clinical response to ATT in a patient with fever of unknown origin or compatible clinical syndrome with radiographic and histopathological features suggestive of TB, including tissue sample with granulomas; and (3) presence of MTB DNA using PCR.

Pre-transplant screening of donor and recipient for TB infection should be rigorous given the high risk of TB in the transplant setting and significant associated mortality. In transplant candidates and living donors, thorough history taking and comprehensive physical examination should be performed with a special focus on the medical and social risk factors for TB mentioned earlier. History of TB exposure is most essential and one should inquire about residence and travel history to endemic areas, contact with a known active TB case, and prior TST testing results. In patients with a history of prior LTBI or TB, details regarding treatment regimen and duration are essential, and active TB in these individuals should

be excluded. These patients may need additional testing and consultation with a transplant infectious disease specialist. Donors with active TB within 2 years have higher risk of relapse and transmission *via* the allograft[6]. Patients without prior history of known LTBI or TB disease should undergo testing for LTBI with a PPD test or IGRA. If the first PPD test is negative, a second skin test is recommended for booster effect as discussed earlier. A CXR is part of routine preoperative screening and should be evaluated for evidence of prior granulomatous disease. Patients with positive PPD or IGRA should be treated for LTBI prior to transplantation, whenever possible, after exclusion of active TB. Individuals with low risk of TB based on history and negative testing are cleared for transplantation. In high risk patients with negative TST/IGRA, indeterminate IGRA or chest imaging suggestive of prior granulomatous disease, it is recommended to treat with INH for presumed LTBI, prior to transplantation. Active TB needs to be ruled out by appropriate smears, cultures and molecular testing before treatment for latent TB is initiated. In high-risk patients, urine for AFB and renal imaging should also be performed to rule out genitourinary TB[19]. In our case series, two patients had known LTBI by PPD/IGRA but did not receive INH prophylaxis prior to the transplant. One of the patients received INH prophylaxis immediately post-transplant. One patient was not tested for LTBI, but was high risk based on prior exposure history and a CXR with old granulomatous changes. Interestingly, one recipient tested negative by IGRA and was low clinical risk. He had calcified nodules on imaging and later developed TB disease.

Pre-transplant evaluation is challenging in deceased donors given the limited history available. Efforts should be made to obtain a history regarding prior TB exposure, TB disease and treatment from family and healthcare givers. The evaluation is similar to living donors as above, prior to accepting the organ. In donors with a history of TB and reliable information about completed ATT, appropriate smears, cultures and molecular testing should be done to rule out active disease. In deceased donors with a history of TB disease and insufficient information about treatment or positive testing, it is recommended to reject the donor except in urgent transplants. In this scenario, recipients should be treated for active TB after informed consent with close monitoring under the guidance of an infectious disease specialist[6,8].

Management

Direct evidence regarding management of transplant recipients for prevention and treatment of latent and active TB infection is lacking. Their care is largely based on expert opinion and extrapolation from studies in immune-competent and other immunocompromised populations. Indications for treatment of LTBI in recipient candidates include a positive TST/IGRA as well as those with a negative TST/IGRA or indeterminate IGRA with risk factors: Radiographic evidence of prior TB in the absence of treatment, donor with recent TB exposure, positive TST or radiographic signs, or close prolonged contact with an active TB case[8]. Before treatment of LTBI, active TB needs to be excluded. One recipient in our case series with a positive PPD received INH prophylaxis soon after transplant for 9 mo. However, a month after finishing INH, she developed renal allograft TB. This patient was asymptomatic, but cultures were not obtained prior to initiation of prophylaxis. The other explanations for the development of active TB include possible low levels of INH due to concomitant steroids and inadequate host response in the setting of immunosuppressant use post-transplant. Treatment regimens for LTBI include INH 5 mg/kg daily (maximum dose 300 mg/d) for 9 mo with pyridoxine 25-50 mg daily to prevent neurotoxicity. INH 15 mg/kg twice weekly (maximum dose 900 mg/d) with pyridoxine, given as directly observed therapy has also been proposed. Rifampin 10 mg/kg daily (maximum dose 600 mg/d) for four months may be used prior to transplant but should be avoided if possible after transplant due to drug interaction with the immunosuppressant medications. Combination of pyrazinamide and rifampin daily for 2 mo is not recommended due to the high risk of hepatotoxicity in the transplant population. A shorter regimen of weekly INH and rifapentine for 12 wk, as directly observed therapy, to treat immune competent individuals is not recommended in renal transplant candidates[8]. Compliance with LTBI treatment is poor as seen in a North American study where only half of the patients initiated on therapy finished the complete course of treatment[6]. If treatment is interrupted for more than two months, patients should be excluded again for active TB[12]. Adverse effects are more common in solid organ transplant recipients with hepatotoxicity seen in 37% of kidney recipients and up to 50% in liver transplant recipients[8,20]. Monitoring should involve monthly physician examination and bi-monthly blood levels of liver function tests.

Medications will need to be discontinued or dose adjusted if liver function tests are more than three times the upper limit of normal with symptoms/signs, or more than five times the upper limit of normal without symptoms[12].

Treatment of active drug susceptible TB usually involves two months of an initial phase therapy with INH, rifampin/rifabutin, pyrazinamide, +/- ethambutol, followed by a continuation phase therapy of four months of INH and rifampin, with a total duration for six months. Cavitary TB, with positive sputum culture after two months of intensive phase therapy, is treated for nine months' duration with prolongation of continuation phase therapy. Bone and joint disease as well as severe disseminated disease are treated for a total of six to nine months. Central nervous system disease warrants treatment duration of nine to twelve months[8]. Since the majority of transplant recipients present with severe disseminated TB, 9 mo or longer duration of treatment may be preferred in the presence of response to ATT. Risk of recurrence was found to be lower when treatment is extended to beyond 12 mo[12]. Longer course of therapy is required if second line drugs are used

due to adverse effects or in cases of drug resistant TB.

MDR and extensively drug resistant TB fortunately has been rarely reported in solid organ transplant recipients. This should be treated according to drug susceptibility testing with at least four active drugs. The World Health Organization (WHO) suggests a total treatment duration of 18 mo after culture conversion. Adjunctive surgery may be required in some patients[12].

In the United States, patients with pulmonary TB have sputum cultures obtained monthly until two consecutive cultures are negative, and at two months of intensive phase therapy to further guide treatment. If the sputum culture at two months of treatment is positive, WHO recommends sputum smear microscopy at the end of the third month and if positive, sputum culture and drug susceptibility testing. Drug susceptibility testing should also be done if a patient develops positive cultures after a period of negative cultures. European guidelines in transplant recipients recommend sputum smear and culture at a minimum of two months and four months of treatment, at the end of ATT, and on two further occasions until the end of 12 mo[12]. Extra-pulmonary TB in general is followed clinically. Patients should have baseline laboratory data including a comprehensive metabolic panel, complete blood counts, and uric acid levels. They should be monitored and managed for hepatotoxicity as described above. Baseline and monthly visual acuity and red-green discrimination testing should be done with ethambutol use.

If one suspects pulmonary TB, the patient should be isolated in a negative pressure room until active TB is excluded. Pulmonary TB patients should be isolated for at least two weeks with clinical improvement on therapy and until three consecutive negative sputum smears are obtained. In immunocompetent patients, rapid testing with Xpert MTB/Rif has been used in conjunction for decisions regarding discontinuation of TB isolation. However, this cannot be recommended in the transplant population at this time.

Drug interactions

Patients need to be monitored closely for drug interactions with immunosuppressive medications used in solid organ transplant given the increased risk of rejection. Rifampin is used in treatment of TB due to its potent MTB sterilizing action. Rifampin is a strong inducer of CYTP3A4 leading to increased metabolism of calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, mycophenolate mofetil and corticosteroids. Rifabutin is a less potent cytochrome inducer. Drug levels need to be monitored closely at initiation of TB therapy, after discontinuation of rifampin or rifabutin, or with any adjustment of immunesuppressant dosing[8]. Spanish guidelines recommend rifamycin free regimens for treatment, except for disseminated TB and INH resistant TB[19]. We prefer rifamycin based regimens for treatment of TB in our renal transplant recipients. Other drug interactions to consider include the following: INH may increase corticosteroid levels and its adverse effects, streptomycin with cyclosporine and sirolimus may cause additive nephrotoxicity, fluoroquinolones can further increase risk of tendon rupture with concomitant corticosteroids, and corticosteroids may decrease INH levels[12].

Complications

Complications of TB besides primary organ involvement include septic shock, venous thromboembolism (VTE), immune reconstitution inflammatory syndrome (IRIS) and macrophage activation syndrome (MAS) or hemophagocytic syndrome[21,22]. Septic shock with TB is associated with high mortality[23]. Pulmonary and extra-pulmonary TB both predispose to VTE with the risk being much higher than other hospitalized patients, in general[24,25]. IRIS is recognized by the paradoxical symptom worsening of fever, cough, enlarging lymph nodes or worsening of findings on imaging after initiation of treatment. This is seen primarily in the first few months of initiation of therapy. MAS is rare and has high mortality. It manifests as fever, hepatosplenomegaly, pancytopenia and liver abnormalities. Diagnosis is usually made by bone marrow biopsy showing infiltration of non-malignant macrophage phagocytizing red blood cells[12,21]. In our case series, one patient presented with septic shock and presumed MAS succumbing to his illness. The other patient presented with VTE and developed IRIS two months after initiation of ATT.

In conclusion, TB remains a challenging opportunistic infection in the solid organ transplant population. Efforts should be made to prevent active TB *via* recognition and treatment of LTBI in potential donors and transplant candidates, ideally prior to transplantation. Current tests for LTBI (PPD and IGRA) can be falsely negative in patients with ESRD and those on immunosuppressive medications. IGRA has not been evaluated for use in deceased donors. There is a need for better diagnostics for LTBI. Exclusion of active TB is of paramount interest prior to LBTI therapy by culture, smear, imaging and molecular testing as needed. Given the changes in the allocation system, older and longer dialysis vintage recipients are being transplanted, increasing the risk of active TB. Due to the organ shortage with more high risk donors being utilized, the risk for donor derived TB might increase as well. More widespread use of rapid NAA assays and line probe assays is needed to screen high-risk TB donors, and for diagnosis of TB in recipients. As disseminated and extra-pulmonary disease are more common in transplant recipients, studies are needed to assess the performance of NAA assays in body fluids, other than sputum, in this population. Given diagnostic limitations, physicians need to maintain a high clinical suspicion for TB post transplantation in order to initiate early treatment and decrease morbidity and mortality. Studies are needed to investigate the efficacy of shorter treatment regimens given the interactions with immunosuppressive medications and significant adverse effects. Lastly, public health efforts are needed both at the

global and domestic level to minimize this disease.

COMMENTS

Case characteristics

Four kidney transplant recipients, aged 38-67 years, presenting with fever within one year of kidney transplantation.

Clinical diagnosis

Lymphadenopathy, pleural effusion, pericardial effusion, acute respiratory failure, septic shock, acute kidney injury, bilateral lower extremity deep venous thrombosis and pulmonary embolism.

Differential diagnosis

Bacterial infections, fungal infections such as histoplasmosis, cryptococcosis, interstitial nephritis due to adenovirus infection, post-transplant lymphoproliferative disorder.

Laboratory diagnosis

Demonstration of acid-fast bacilli in sputum and bronchoalveolar lavage. Mycobacterium tuberculosis grew in cultures from sputum, blood, lymph node aspirate and pericardial fluid. Positive Mycobacterium tuberculosis PCR in blood and bronchoalveolar lavage.

Imaging diagnosis

Radiological features included calcified/non-calcified lung nodules, diffuse lung infiltrates, pleural effusion, lymphadenopathy, pulmonary embolism and increased flurodeoxyglucose uptake in the kidney allograft on positron emission tomography scan.

Pathological diagnosis

Necrotizing and non-necrotizing granulomas seen on kidney allograft and transbronchial lung biopsies respectively. Demonstration of acid-fast bacilli on lung biopsy.

Treatment

Two months of Rifampin, Isoniazid, Ethambutol and Pyrazinamide followed by 4 mo of Rifampin and Isoniazid. Second-line drugs moxifloxacin and amikacin were used in selected cases.

Related reports

Tuberculosis in solid organ transplant recipients is rare in the developed countries. A study in 1998 estimated 0.35%-1.2% incidence in the United States.

Term explanation

Tuberculosis is a rare opportunistic infection caused by acid fast bacillus Mycobacterium tuberculosis that was identified by Robert Koch in 1884.

Experiences and lessons

Tuberculosis should be considered in solid organ transplant recipients presenting with unexplained fever to avoid delayed or missed diagnosis. TB carries high morbidity and mortality. Transplant recipients should have comprehensive screening for risk factors for TB along with testing for latent TB. Active TB needs to be ruled out prior to the treatment of latent TB. Ideally patients should be treated for latent TB prior to transplant due to drug interactions and suboptimal response to therapy in the setting of immunosuppression.

Peer-review

The data across the different trials is reviewed well. The benefits and adverse effects are clearly illustrated and summarized.

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