Disseminated tuberculosis in a lung transplant recipient presenting as tenosynovitis, subcutaneous nodules, and liver abscesses

Lilian Vargas Barahona1, José Henao-Cordero1, Joshua Smith, Alice Gray, Carrie B. Marshall, Sias Scherger, Valida Bajrovic and Yiannis Koullias

Abstract: Tuberculosis is of particular concern in lung transplant recipients. We present the case of a patient who received a double lung transplant from a deceased donor from Mexico and developed disseminated tuberculosis 60 days post-transplant manifested as tenosynovitis, liver abscesses, and subcutaneous nodules with no definitive lung allograft involvement. The recipient did not have evidence of tuberculosis on explanted lungs, had a negative interferon gamma release assay pre-transplant, and did not have risk factors for this infection. Mycobacterium tuberculosis should remain in the differential diagnosis of early post-transplant infections with atypical presentations, evidence of dissemination, or lack of improvement with appropriate antimicrobial coverage, even in the absence of typical lung findings.

Keywords: lung transplant, mycobacterium infections, organ donation, tenosynovitis, tuberculosis, tuberculosis screening

Received: 12 August 2022; revised manuscript accepted: 23 September 2022.

Introduction

Tuberculosis (TB) is a leading cause of morbidity worldwide. In the United States, the incidence of active TB remains low with most cases occurring in people born outside the country. Most cases in the United States result from untreated latent tuberculosis infection (LTBI), which is not a reportable infection.1

Solid organ transplant (SOT) recipients are at risk for active TB with an incidence of 20–74 times higher than the general population.2,3 SOT recipients have higher risk of death,4 risk of graft dysfunction, and frequently have therapy limitations due to hepatotoxicity and drug–drug interactions.2,5 Disseminated infection is associated with higher mortality4 and occurs in 22–39% of transplant recipients with active TB.6

Early detection of TB on SOT recipients can be challenging due to protean clinical presentations. We present the case of a lung transplant recipient with disseminated TB that presented as tenosynovitis, subcutaneous nodules, and hepatic abscesses without evident lung graft involvement. We describe previous cases of tuberculous tenosynovitis in SOT. We highlight limitations in screening of TB in solid organ recipients and donors and the importance of recognizing TB in the differential diagnosis of disseminated infections on immunocompromised hosts.

Case presentation

A 60-year-old White, non-Hispanic woman with history of bilateral lung transplant due to severe emphysema presented with painful occipital subcutaneous nodules and a painful right index finger 60 days post-transplant. Induction immunosuppression consisted of basiliximab and maintenance immunosuppression was prednisone, tacrolimus, and mycophenolate. Histologic examination of native lungs showed changes related to smoking (severe emphysema and bronchiolitis),
bronchiectasis, and non-necrotizing granulomatous inflammation suggestive of hypersensitivity pneumonitis. Acid-fast bacilli (AFB) and Grocott Methenamine Silver (GMS) stains were negative for organisms. Two days after transplant, the right lung graft was removed due to lobar torsion and infarction. Histologic examination of explanted graft confirmed infarction and AFB stains were also negative. Patient was discharged home on post-operative day 13. Thirty days post-transplant she had declining pulmonary function tests and was treated for presumed rejection with high-dose methylprednisolone for 3 days and rituximab due to presence of donor-specific antibodies. She developed parainfluenza infection on post-transplant day 54 and received methylprednisolone and intravenous immunoglobulin. Sixty days post-transplant she developed painful nodes in the occipital area and painful swelling of the right index finger. Two weeks later, she presented to clinic and was started on linezolid and ceftriaxone for cellulitis. Shortly after completing a 2-week course of antibiotics, pain worsened and she developed nausea, vomiting, chills, and diaphoresis prompting hospital admission. Social history was notable for residing in Kansas, and never having lived or traveled outside the United States. She had dogs and cats but denied bites or scratches. She denied exposure to livestock or other animals, recent water exposures, remote traumatic injuries, gardening, or other outdoor work. She denied consumption of unpasteurized dairy products. She had no history of incarceration or homelessness.

On examination, she was afebrile and well-appearing. She had two exquisitely tender, non-mobile nodules in her occiput without overlying skin discoloration or drainage. There was no cervical, axillary, or inguinal lymphadenopathy. Her right index finger was edematous and erythematous, with limited range of motion. Right-sided breath sounds were absent and left lung was clear to auscultation. There was no abdominal tenderness, hepatosplenomegaly, or rash. Laboratory studies were notable for leukopenia with $3 \times 10^9$ cells/liter with lymphopenia of $0.6 \times 10^9$ cells/liter.

Non-contrast chest computed tomography showed new, numerous hypoattenuating liver lesions. Abdominal magnetic resonance imaging (MRI) showed multiple rim-enhancing hepatic lesions suggestive of multifocal abscesses. Right-hand MRI showed a peripherally enhancing 1.3-cm fluid collection along the palmar aspect of the index finger associated with the flexor tendon sheath. Transthoracic echocardiogram and brain MRI were unremarkable. Extensive infectious work-up remained negative.

The patient underwent core needle biopsy of liver lesions and finger incision and drainage. Direct staining of finger tissue was positive with 1–9 acid fast bacilli (AFB)/10 high-power field and empiric treatment for disseminated non-tuberculous mycobacteria (NTM) with linezolid, cefoxitin, azithromycin, and moxifloxacin was promptly initiated. Both liver and tendon histopathology noted granulomatous inflammation with AFB (Figures 1 and 2). Finger and liver tissue cultures grew AFB after 4 days identified by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry as Mycobacterium tuberculosis complex. Antimicrobial susceptibility testing was performed, and isolate showed susceptibility to ethambutol, isoniazid, pyrazinamide, and rifampin. The patient was started on TB induction therapy with rifabutin (to avoid interaction between rifampin and tacrolimus), isoniazid, pyrazinamide, and ethambutol. AFB sputum, blood, and urine cultures remained negative after 8 weeks. Mycophenolate was held and prednisone and tacrolimus were continued. Patient received 2 months of 4-drug induction treatment followed by 10 months of rifabutin and isoniazid for a total of 12 months of treatment.

The organ donor was originally from Mexico and did not have known medical history. The cause of death was cerebral hemorrhage. There was no information available regarding prior TB testing or treatment. No other recipients have thus far developed TB.

**Discussion**

TB represents a difficult infection to diagnose and treat in SOT recipients with grave implications for morbidity including graft failure and mortality. Up to 95% of active TB cases occur within the first-year post-transplant, with 50–76% of these cases involving the lungs.3-7,10-12 Lung transplant recipients are at greater risk of graft TB infection as the lung is the primary site of infection.3,10-12 Disseminated infection is associated with higher mortality4,13 and occurs in 22–39% of transplant recipients with active TB, a stark contrast with the relatively low incidence of disseminated infection in the general population.
Diagnosing active TB in patients with SOT is challenging due to the often unusual and non-specific symptoms, leading to a substantial delay in diagnosis compared to the general population.\textsuperscript{4,7} The most common symptom of active TB in SOT recipients is fever, but cough and weight loss are also seen. Other manifestations of involvement can be esophagitis, sacroiliitis, dactylitis, skin nodules, and laryngitis.\textsuperscript{14}
The sites of involvement in this case are uncommon for TB, yet tuberculous tenosynovitis has been described as a site for extrapulmonary infection (Table 1). Infectious tenosynovitis of the digits is more frequently associated with NTM or other bacteria typically after traumatic inoculation; hence, in SOT, recipients should prompt biopsy for histopathologic evaluation due to risk of infection with atypical pathogens.

The most common mechanism of developing active TB after SOT is reactivation of recipient LTBI. Exposure after transplant is more common in TB endemic areas and transmission from donors is uncommon with <5% of cases. Thirty-six cases of donor-derived TB, of which 16 were lung transplants, have been reported. Some reports note that donor-derived infections (DDIs) tend to occur in the early post-transplant period (within 3 months) and graft involvement is almost universal. The risk of developing TB post-transplant from a living donor with LTBI is not well established and some studies suggest it may not be significant.

The mechanism of acquisition of infection in this patient is not clear. Recipient pre-transplant screening was notable for a negative interferon gamma release assay (QuantiFERON-TB Gold Plus), absence of risk factors for TB, and residency in a low prevalence area. Native lung histopathology did not have features of infection. Bronchoscopy was not performed post-transplant due to pneumonectomy; however, expectorated sputum cultures were negative for AFB and there was no radiographic evidence of TB in the graft. Right pneumonectomy histopathology (donor lung) did not have features of infection either. These findings raise suspicion for possible donor transmission from latent infection; however, recipient reactivation despite a negative interferon-γ release assay (IGRA) cannot be completely excluded.

Although donor-derived transmission cannot be confirmed in this case, the possibility illustrates the importance of identifying donors at higher risk for TB to reduce DDI, especially in lung transplant recipients. Evaluation for TB in transplant candidates and living donors is well established. Recommendations for deceased donors include relying on review of medical history, exposures, prior IGRA or tuberculin skin test (TST), and radiographic findings. It is unclear whether this clinical information is readily available at the time of organ procurement. Furthermore, TST is not a feasible test for deceased donors, while IGRA lacks performance data in this setting, with relatively high rates of indeterminate results which may be uninterpretable. More studies are needed to understand the risk of transmission of TB from unrecognized LTBI in deceased donors.

| Author | SOT | Onset of symptoms after transplant | Other organ involvement | Immunosuppression | Treatment | Recipient risk factors for TB |
|--------|-----|----------------------------------|------------------------|-------------------|-----------|---------------------------|
| Le Meur et al. | Heart | 4 months | No | Cyclosporine, Steroids | RIF + INH + EMB + PZA | Travel to sub-Saharan Africa |
| Jha et al. | Renal | 4 years | Tonsils | Cyclosporine, azathioprine, prednisolone | INH + PZA + EMB + CPFX | From India |
| Munoz et al. | Renal | 6 years | No | Cyclosporine, Mycophenolate | Surgery | Daughter LTBI |
| Toyokawa et al. | Liver | 8 years | Lungs | Tacrolimus, Mycophenolate | INH + EMB + RIF | Not described |

CPFX, ciprofloxacin; EMB, ethambutol; INH, isoniazid; LTBI, latent tuberculosis infection; LVX, levofloxacin; PZA, pyrazinamide; RIF, rifampin; SOT, solid organ transplant.
The most common risk factor for DDI is having a donor from an endemic region.6 Currently, the US TB screening pathway does not specify information about country of origin only citizenship status which may be unhelpful to identify those at higher risk.23 With increasing mobility of populations globally, the increased diversity of the organ donor pool will result in a changing epidemiology of DDI.

This case highlights the importance of having a high index of suspicion for TB in the early post-transplant period, particularly in lung recipients, even in low-prevalence areas. Clinical manifestations can be largely atypical and unspecific, with dissemination and absence of pulmonary involvement.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The patient has provided written consent for publication.

Author contributions
Lilian Vargas Barahona: Conceptualization; Writing – original draft; Writing – review & editing.
José Henao-Cordero: Writing – review & editing.
Joshua Smith: Writing – review & editing.
Alice Gray: Writing – review & editing.
Carrie B. Marshall: Visualization; Writing – review & editing.
Sias Scherger: Writing – review & editing.
Valida Bajrovic: Writing – review & editing.
Yiannis Koullias: Conceptualization; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

ORCID iDs
Lilian Vargas Barahona https://orcid.org/0000-0003-3330-808X
José Henao-Cordero https://orcid.org/0000-0002-1947-8675

References
1. Langer AJ, Navin TR, Winston CA, et al. Epidemiology of tuberculosis in the United States. Clin Chest Med 2019; 40: 693–702.
2. Subramanian AK, Theodoropoulos NM and Infectious Diseases Community of Practice of the American Society of Transplantation. Mycobacterium tuberculosis infections in solid organ transplantation: guidelines from the infectious diseases community of practice of the American Society of Transplantation. Clin Transplant 2019; 33: e13513.
3. Torre-Cisneros J, Doblas A, Aguado JM, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) Cohort. Clin Infect Dis 2009; 48: 1657–1665.
4. Benito N, García-Vázquez E, Horcajada JP, et al. Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: a retrospective matched cohort study. Clin Microbiol Infect 2015; 21: 651–658.
5. Abad CLR and Razonable RR. Mycobacterium tuberculosis after solid organ transplantation: a review of more than 2000 cases. Clin Transplant 2018; 32: e13259.
6. Abad CLR and Razonable RR. Donor derived Mycobacterium tuberculosis infection after solid-organ transplantation: a comprehensive review. Transpl Infect Dis 2018; 20: e12971.
7. Bodro M, Sabé N, Santín M, et al. Clinical features and outcomes of tuberculosis in solid organ transplant recipients. Transpl Proceed 2012; 44: 2686–2689.
8. Rungruanghiranya S, Ekpanyaskul C, Jirasiritum S, et al. Tuberculosis in Thai renal transplant recipients: a 15-year experience. Transplant Proc 2008; 40: 2376–2379.

9. Mamishi S, Pourakbari B, Moradzadeh M, et al. Prevalence of active tuberculosis infection in transplant recipients: a systematic review and meta-analysis. Microb Pathog 2020; 139: 103894.

10. Mortensen E, Hellinger W, Keller C, et al. Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. Transpl Infect Dis 2014; 16: 67–75.

11. Bravo C, Roldán J, Roman A, et al. Tuberculosis in lung transplant recipients. Transplantation 2005; 79: 59–64.

12. Guirao-Arrabal E, Santos F, Redel-Montero J, et al. Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of mTOR inhibitors and azathioprine use. Transpl Infect Dis 2016; 18: 512–519.

13. Singh N and Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis 1998; 27: 1266–1277.

14. Nasir N, Surfaraz S, Khanum I, et al. Tuberculosis in solid organ transplantation: insights from TB endemic areas. Curr Infect Dis Rep 2021; 23: 14.

15. Le Meur A, Arvieux C, Guggenbuhl P, et al. Tenosynovitis of the wrist due to resistant Mycobacterium tuberculosis in a heart transplant patient. J Clin Microbiol 2005; 43: 988–990.

16. Jha V, Hayat A, Nahar U, et al. Tubercular tonsillitis and tenosynovitis in a renal transplant recipient. Transplantation. 2003; 76: 269–270.

17. Muñoz P, Rodriguez M, Giannella M, et al. A painful hand in a kidney transplant recipient. Nephrol Dial Transplant 2006; 22: 971–972.

18. Toyokawa N, Kokubu T and Fujioka H. Mycobacterial tuberculous tenosynovitis of the extensor tendon occurring after liver transplantation: a case report. Hand Surg 2008; 13: 37–40.

19. Abad CL and Razonable RR. Prevention and treatment of tuberculosis in solid organ transplant recipients. Expert Rev Anti Infect Ther 2020; 18: 63–73.

20. Hernández-Hernández E, Alberú J, González-Michaca L, et al. Screening for tuberculosis in the study of the living renal donor in a developing country. Transplantation 2006; 81: 290–292.

21. Alrajhi AA, Alotaibi J, Alghamdi AM, et al. Mycobacterium tuberculosis DNA in living donor transplanted livers and donor-related tuberculosis in recipients: a retrospective longitudinal cohort study. Transpl Infect Dis 2020; 22: e13212.

22. Morris MI, Daly JS, Blumberg E, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. Am J Transplant 2012; 12: 2288–2300.

23. Kumar D, Budev M, Koval C, et al. Donor-derived tuberculosis (TB) infection in lung transplant despite following recommended algorithm. Am J Transplant 2013; 13: 2225–2226.