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Paradoxical immune reconstitution inflammatory syndrome associated with disseminated tuberculosis infection in an unrelated donor cord blood transplant recipient

Yeon Joo Lee^{1,4}, Melissa Bacchus¹, Elizabeth Schmidt¹, Mohit Chawla^{2,4}, Juliet N. Barker^{3,4}, Genovefa A. Papanicolaou^{1,4}

¹Infectious Diseases Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

²Pulmonary Service, Department of Medicine, Memorial Sloan Kettering Cancer Center

³Adult Bone Marrow Transplantation Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

⁴Weill Cornell Medical College, New York, NY

Abstract

Tuberculosis (TB) is an infrequent infection after hematopoietic cell transplant (HCT), with associated mortality up to 30%. The utility of universal screening for latent TB in HCT candidates is controversial due to the lack of sensitive screening tests. We describe a case of disseminated TB infection complicated by immune reconstitution inflammatory syndrome in an adult double unit umbilical cord blood transplant recipient who originated from the United Arab Emirates.

Keywords

Tuberculosis; Immune reconstitution inflammatory syndrome; Hematopoietic cell transplant

INTRODUCTION

Tuberculosis (TB) is an infrequent but serious infection after hematopoietic cell transplant (HCT) with associated mortality up to 30%.^{1,2} Timely diagnosis of TB can be challenging in HCT recipients.² TB may be present with extrapulmonary manifestations or mimic post-transplant complications such as graft versus-host disease (GVHD) or Epstein-Barr virus-associated post-transplant lymphoproliferative disease.³ Thus a high index of suspicion is needed to establish a timely diagnosis. Management of TB in HCT recipients is also challenging. HCT recipients are often on multiple concomitant medications which can alter the pharmacokinetics of anti-tuberculous medications or may have impaired absorption due to gastrointestinal GVHD.

Corresponding Authors: Yeon Joo Lee, MD, MPH, Assistant Attending, Infectious Diseases Service, Department of Medicine, 1275 York Ave, Box 9, New York, NY, Phone: 212-639-8180, leey3@mskcc.org.

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Immune reconstitution inflammatory syndrome (IRIS) is a complication of TB therapy. In non-human immunodeficiency virus (HIV) infected patients, rates of IRIS range from 10%-18%^{4,5} while in HIV patients rates of 8%-54% have been reported.⁶ TB-IRIS was reported in 14% in solid organ transplant recipients.^{7,8} TB-IRIS has not been reported after HCT. We report a TB-IRIS in a cord blood transplant (CBT) recipient.

CASE

A 40-year-old man with an acute myelogenous leukemia and diabetes mellitus was transferred to Memorial Sloan Kettering Cancer Center (MSKCC) for a double unit CBT. He was born and resided in the United Arab Emirates (UAE). He denied TB exposure or Bacillus Calmette-Guerin (BCG) vaccination. Pre-transplant positron emission tomography-CT (PET-CT) due to history of perirectal abscess revealed two mildly fludeoxyglucose (FDG) avid subcentimeter left paratracheal lymph nodes (LNs) suggesting inflammatory process. He received conditioning with Cyclophosphamide, Fludarabine, Thiotepa, and total body irradiation without anti-thymocyte globulin, followed by CBT. Mycophenolate mofetil and Cyclosporine-A were administered from day -3 for GVHD prophylaxis. On day +9 post-transplant, he developed dyspnea and chest CT showed new bilateral nodular densities. On day +10, bronchoscopy was performed. Bacterial, mycobacterial, and fungal cultures, *Pneumocystis jiroveci* PCR and galactomannan in the bronchoalveolar were negative. He received corticosteroids with improvement in symptoms and radiographic resolution in follow-up chest CT.

His post-transplant course was complicated by several readmissions for treatment of gastrointestinal GVHD by treated with corticosteroids. Approximately 2.5 months post-transplant, he developed intermittent fevers requiring inpatient work-up. Multiple blood cultures for bacteria and mycobacterium and trans-thoracic echo were negative. Sinus/chest/abdominal-pelvic CT showed increased left upper paratracheal LNs as 1.3x1.2cm from 1.2x1.1cm. On day +154, PET-CT was performed for work-up of fever of unknown origin (Figure 1a). PET-CT showed an increase in size of left paratracheal lymphadenopathy seen in pre-transplant PET-CT. QuantiFERON-TB Gold (Mayo Medical Laboratories, Rochester, MN) was positive. He underwent real-time endobronchial ultrasound transbronchial needle aspiration of the left paratracheal LN. Cytology showed polymorphous lymphoid population with necrosis and acid-fast organisms and *Mycobacterium tuberculosis* complex (MTB) PCR was positive. Further travel history revealed prior travel to Syria.

Isoniazid 300mg, rifabutin 300mg, pyrazinamide 1500mg, and ethambutol 1200mg (RIPE) all given orally daily were started. Patient's compliance was monitored by the New York City Department of Health. TB sensitivity testing (Wadsworth Center, Albany, NY) showed sensitivity to all 4 drugs. He, however, continued to have intermittent fever, nausea and vomiting which required multiple additional hospital admissions. After 1.5 months of anti-tuberculous treatments, he was admitted to hospital due to fever, back pain, left leg pain, nausea, and vomiting. A follow-up PET-CT showed increased size of FDG avid left upper paratracheal nodes, new FDG avid left supraclavicular node (0.6x0.5 cm), new multifocal hepatic and splenic involvement, and new solitary subcutaneous soft tissue nodule on his left buttock (Figure 1b). In addition, FDG avid foci were noted in the bowel and new FDG

uptake on the left proximal femur and right calcaneus. He remained on RIPE. Endoscopy and colonoscopy were performed with unremarkable findings. Core biopsy on left gluteal lesion performed after 2 months of RIPE showed severe acute inflammation with necrotic debris. Acid-fast Bacilli (AFB) stains showed scattered AFB, but MTB PCR and mycobacterial culture were negative.

Due to concern for suboptimal exposure to RIPE related to gut GVHD and concomitant immunosuppressants, TB drug levels were obtained (National Jewish Health, Denver, Colorado) and levels were below expected range for all 4 drugs. After approximately 3 months of RIPE, TB drugs were adjusted to isoniazid 300mg, rifabutin 450mg, and moxifloxacin 400mg. Clinical course, immunosuppressants and antituberculous treatment are shown on Figure 2. He was clinically well after 12 months of anti-tuberculous treatment (Figure 1c) and all therapy was stopped at 12 months. He remains well and in remission 2 years 5 months after transplant.

DISCUSSION

We report a disseminated TB infection with IRIS in a CBT recipient. The patient's clinical course supports IRIS based on worsening clinical presentation while on anti-tuberculous medications and lack of growth of mycobacterium tuberculosis from culture of a new lesion while on anti-tuberculous medications.

The present case illustrates the complexity of diagnosis and treatment of TB in HCT recipients. The American Society of Bone Marrow Transplantation recommends evaluation of HCT candidates at risk for TB.⁹ Tuberculin skin test (TST) is not widely used due to low sensitivity for detecting latent TB in immunocompromised patients.^{10,11} Interferon-gamma release assays (IGRAs) have been used for screening latent TB in immunocompromised patients with improved sensitivities compared to TST.^{12,13} Indeterminate IGRA results are more frequent in immunocompromised patients and children.^{12,14}

At MSKCC, only 8 HCT recipients (0.5%, 8/1708) were diagnosed with TB from 2001 and 2015. At our institution, we recommend screening for latent TB pre-transplant only for patients who have lived in intermediate or high TB endemic countries, or those with history of TB exposure. The incidence of TB in the UAE is 1.8 per 100,000 people in 2013 which is comparable to the US (3.0 per 100,000 people in 2014). Based on our initial evaluation, the patient did not meet criteria for QuantiFERON-TB Gold screening. Retrospectively the patient would have met criteria for screening based on history of travel to Syria. We urge vigilance for detailed history of potential TB exposures. The negative predictive value of QuantiFERON-TB gold is lower in immunosuppressed patients. We recommend a high index of suspicion for TB in patients with compatible symptoms despite a negative QuantiFERON-TB Gold pre-transplant.

Diagnosis and treatment of TB in HCT recipients is challenging. Extrapulmonary tuberculosis or disseminated tuberculosis at the time of diagnosis has been reported and may adversely affect outcome.^{2,15} Due to drug interaction especially with calcineurin inhibitors, rifampin is often replaced with rifabutin. Absorption may also be impaired after HCT due to

GVHD or gastrointestinal complications. We measured TB drug levels when our patient's clinical presentations were worsening. Drug levels for RIPE were low. After 3 months of RIPE, treatments were changed to isoniazid 300mg, rifabutin 450mg and moxifloxacin 400mg.

TB-IRIS has not been reported in HCT recipients. The mechanism of TB-IRIS is uncertain but rapid expansion of TB-specific CD4⁺ T-cell responses with increase in interleukin-6 is a proposed mechanism in HIV infected patients.¹⁶ The reversal of anti-inflammatory to pro-inflammatory responses as a result of withdrawal of immunosuppression along with initiation of antimicrobial therapy is suggested mechanism of IRIS after solid organ transplant.^{7,17} After HCT, the recovery of T-cell function can take months to years.^{18,19} This might in part explain the rarity of IRIS after HCT.

In conclusion, we report a case of paradoxical IRIS associated with disseminated TB in a HCT recipient. TB should be considered in the differential diagnoses for fever of unknown origin post-transplant. Diagnostic tools for latent TB or TB validated in HCT patients may enable more timely diagnosis of this life-threatening infection post-transplant.

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REFERENCES

1. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* 1998;27:1266–1277. [PubMed: 9827281]
2. Cordonnier C, Martino R, Trabasso P, et al. Mycobacterial infection: a difficult and late diagnosis in stem cell transplant recipients. *Clin Infect Dis* 2004;38:1229–1236. [PubMed: 15127333]
3. Ahmed P, Anwar M, Khan B, et al. Role of isoniazid prophylaxis for prevention of tuberculosis in haemopoietic stem cell transplant recipients. *J Pak Med Assoc* 2005;55:378–381. [PubMed: 16302471]
4. Yu SN, Cho OH, Park KH, et al. Late paradoxical lymph node enlargement during and after anti-tuberculosis treatment in non-HIV-infected patients. *Int J Tuberc Lung Dis* 2015;19:1388–1394. [PubMed: 26467593]
5. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004;59:704–707. [PubMed: 15282393]
6. Bahr N, Boulware DR, Marais S, Scriven J, Wilkinson RJ, Meintjes G. Central nervous system immune reconstitution inflammatory syndrome. *Curr Infect Dis Rep* 2013;15:583–93. [PubMed: 24173584]
7. Sun HY, Singh N. Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. *Clin Infect Dis* 2011;53:168–176. [PubMed: 21690625]
8. Sun HY, Munoz P, Torre-Cisneros J, et al. Mycobacterium tuberculosis-associated immune reconstitution syndrome in solid-organ transplant recipients. *Transplantation* 2013;95:1173–1181. [PubMed: 23435454]
9. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009;15:1143–1238. [PubMed: 19747629]
10. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis* 1993;17:968–975. [PubMed: 8110954]
11. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice

Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017;64:e1–e33. [PubMed: 27932390]

12. Kim EY, Lim JE, Jung JY, et al. Performance of the tuberculin skin test and interferon-gamma release assay for detection of tuberculosis infection in immunocompromised patients in a BCG-vaccinated population. BMC Infect Dis 2009;9:207. [PubMed: 20003535]
13. Kim SH, Song KH, Choi SJ, et al. Diagnostic usefulness of a T-cell-based assay for extrapulmonary tuberculosis in immunocompromised patients. Am J Med 2009;122:189–195. [PubMed: 19185094]
14. Hausteiner T, Ridout DA, Hartley JC, et al. The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of Mycobacterium tuberculosis infection in children correlates with age and immune status. Pediatr Infect Dis 2009;28:669–673.
15. De Assis RA, Kerbaui FR, Rodrigues M, et al. Mycobacterium tuberculosis infection: a rare late complication after cord blood hematopoietic SCT. Bone Marrow Transplant 2009;43:667–668. [PubMed: 19029968]
16. Ravimohan S, Tamuhla N, Nfanyana K, et al. Robust Reconstitution of Tuberculosis-Specific Polyfunctional CD4+ T-Cell Responses and Rising Systemic Interleukin 6 in Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. Clin Infect Dis 2016;62:795–803. [PubMed: 26611774]
17. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 2007;7:395–401. [PubMed: 17521592]
18. Storek J, Geddes M, Khan F, et al. Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol 2008;30:425–437. [PubMed: 18949477]
19. Seggewiss R, Einsele H. Immune reconstitution after allogeneic transplantation and expanding options for immunomodulation: an update. Blood 2010;115:3861–3868. [PubMed: 20215642]

Figure 1.

a. PET-CT prior to anti-tuberculous treatment

Legends: FDG avid left paratracheal lymph nodes measuring 2.2x1.4 cm with SUV 8.5.

b. PET-CT 1.5 months after anti-tuberculous treatment

Legends: Unchanged FDG uptake and mildly increased left paratracheal lymph nodes measuring 2.7x1.5 cm from 2.2x1.4cm with SUV 6.2. New FDG avid soft tissue nodule deep in the left gluteus maximus muscle, measuring 3.3x1.93 cm with SUV 4.3.

c. PET-CT 12 months after anti-tuberculous treatment

Legends: Decreased in FDG avid left paratracheal lymph node measuring 1.1x1.1 cm with SUV 4.0. Decreased in FDG avid subcutaneous left gluteal nodule measuring 1.8x1.0 cm with SUV 2.9.

Abbreviations: PET-CT, positron emission tomography-computed tomography; FDG, fludeoxyglucose; SUV, standarized uptake value

Figure 2. Tuberculosis diagnosis with treatment and concomitant immunosuppressive medications

Legends: Except around 4 months of post-transplant, patient was lymphopenic prior to TB diagnosis. At the time of TB diagnosis, his CD4⁺ was 79 cells/mcL and absolute lymphocyte was 254 cells/mcL. Patient's absolute lymphocyte was within normal range (590 cells/mcL) at the time of TB-IRIS diagnosis.

Abbreviations: MMF, mycophenolate mofetil; CSA, cyclosporin-A; INH, isoniazid; rifabutin³⁰⁰, rifabutin 300mg; rifabutin⁴⁵⁰, rifabutin 450mg; EMB, ethambutol; PZA, pyrazinamide; Bx, biopsy; PET-CT, positron emission tomography-computed tomography; TB, tuberculosis, Dx, diagnosis; ALC, absolute lymphocyte count (reference range, 500-5300 cell/mcL)