

Cutaneous and articular tuberculosis in a renal transplant recipient

**Miguel Moyses-Neto^[1], Daniel Drumond^[1], Giuliano Morgantetti^[2],
Tania Maria Pisi Garcia^[1], Valdes Roberto Bolella^[3] and Elen Almeida Romao^[1]**

[1]. Divisão de Nefrologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil.

[2]. Departamento de Patologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil. [

3]. Divisão de Doenças Tropicais e Infecciosas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil

Abstract

Seven months after undergoing kidney transplantation, a 56-year-old woman presented with papules and ulcers in her right forearm. The patient received antibiotics for 8 months with limited improvement. Eleven months after symptom onset, she presented with acute arthritis in her left knee. Asynovial fluid culture yielded *Mycobacterium tuberculosis*, and a forearm ulcer biopsy showed granulomatous inflammation. After surgical fistulectomy and 12 months of tuberculosis treatment, she was cured. Chronic cutaneous ulcers and articular manifestations in TB are rare, but they should always be considered in the differential diagnosis for immunosuppressed patients. Surgical intervention and prolonged treatment might be necessary.

Keywords: Cutaneous tuberculosis. Articular tuberculosis. Kidney transplant.

INTRODUCTION

More than two-thirds of tuberculosis (TB) cases are concentrated in only 22 countries in the world, including Brazil, where the incidence of TB is approximately 37.5/100,000 habitants¹. In the general population, pulmonary disease is the most frequent presentation. However, in patients who have received solid organ transplants (SOTs), the presentation of TB varies, posing a diagnostic challenge. Between one-third and half of TB cases in patients receiving SOTs occur as extra-pulmonary disease, compared to only 10-15% of cases in immunocompetent hosts. Delays in diagnosis and treatment are natural consequences of these unusual clinical presentations². TB is also an important cause of mortality and morbidity in patients receiving SOTs, and the frequency of active TB in this population is estimated to be 20-74 times that in the general population^{2,3}. Herein, we present the clinical features of a kidney transplant recipient who presented with a cutaneous TB abscess and knee arthritis 7 months after the transplantation

CASE REPORT

A 56-year-old Caucasian woman received a renal transplant from a deceased donor in April 2011 owing to polycystic kidney disease. Before the transplantation, she was on peritoneal dialysis for at least 5 years. The patient received thymoglobulin

to induce immunosuppression and prednisone, tacrolimus, and sodic mycophenolate to maintain it. She had a family history of TB, as her mother was treated for TB 22 years ago, but she did not undergo a tuberculin skin test (TST) before transplantation. Seven months after surgery, she presented to the outpatient clinic with painful violaceous papules that progressed to nodules in the right forearm and edema and pain in her right hand, which were associated with violaceous, diffuse edema in the palm and back of her hand. There was also fluid collection near the wrist and periarticular edema in the right elbow with spontaneous drainage associated with systemic febrile manifestations (**Figure 1A** and **Figure 1B**). Subsequently, laboratory data showed a blood creatinine level of 1.6mg/dL. A diagnosis of tenosynovitis was established, and the patient received treatment with ciprofloxacin and clindamycin; the patient received ciprofloxacin for 4 months. Ultrasonography of the right hand showed tenosynovitis of the flexors and extensors from the first to the fourth compartments associated with heterogeneous fluid collection and inflammation in the proximal area of the forearm. Magnetic resonance images of the hand confirmed the ultrasound findings. The fluid collection was compatible with an abscess in the thenar and interosseous area. A diagnostic puncture drew 20mL of a thick and purulent substance. These procedures were repeated during the 2-month period following the initial symptoms. This collected sample was sent for bacterial and fungal culture, which yielded negative results. Concurrently, the patient presented with intermittent febrile episodes, even after prolonged antibiotic therapy. Surgical drainage was performed in the forearm and wrist area. Samples collected from these abscesses grew *Klebsiella oxytoca* and

Corresponding author: Dr. Miguel Moyses Neto.

e-mail: mimoyeses@gmail.com

Received 19 March 2016

Accepted 7 April 2017

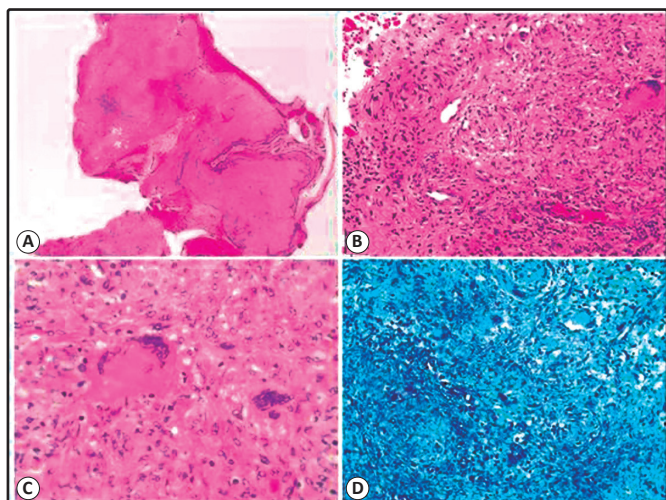


FIGURE 1 - (A): Epidermal ulceration with the formation of granulation tissue associated with a diffuse superficial and deep dermal inflammatory infiltrate (H&E, $\times 20$). **(B):** Mononuclear inflammatory infiltrate with multiple small non-necrotic granulomas and Langerhans-type multinucleated giant cells (H&E, $\times 200$). **(C):** Detailed view of the multinucleated giant cells (H&E, $\times 400$). **(D):** Photomicrograph of the Ziehl-Neelsen stain showing no mycobacteria ($\times 200$). HE: hematoxylin and eosin.



FIGURE 2 - (A) and (B): Ulcers and draining fistulae in the right forearm, palm, and hand before treatment. **(C) and (D):** Post-surgical appearance of the right forearm and hand. **(E) and (F):** Complete regression of the lesion, but with sequelae observed in the right thumb at the end of treatment **(E)**.

Staphylococcus epidermidis on culture. The patient was treated with antibiotics guided by drug susceptibility testing. All of these treatments were administered for at least 3 more months. Eleven months after the initial symptoms, she presented with acute arthritis in her left knee. Ultrasonography of the knee showed arthritis with suprapatellar effusion. Amagnetic resonance image of the knee showed moderate articular effusion with signs of synovitis and capsulitis. This lesion was drained and cultured for bacteria, fungus, and mycobacteria. At this point, skin biopsy of an ulcer in the forearm, which had progressed from a previous nodule, was performed. Histopathology revealed

epidermal necrosis that resulted in skin ulceration with the formation of granulation tissue. The dermis showed a diffuse granulomatous inflammatory infiltrate with small non-necrotic granulomas associated with Langerhans-type multinucleated giant cells. Tests for special stains of mycobacteria, bacteria, and fungi showed negative findings (**Figures 1A,B,C and D**). The synovial fluid culture for pyogenic bacteria and fungus yielded negative results, but the results for *Mycobacterium tuberculosis* using the BACTEC™ Mycobacteria Growth Indicator Tube 960 (MGIT 960) yielded positive results (MGIT 960; Becton Dickinson Diagnostic Systems, Sparks, MD). The isolate was tested via routine molecular tests in the laboratory (Genotype® MTBDR plus; Hain Lifescience, Germany) and showed susceptibility to rifampicin and isoniazid. Chest radiography revealed normal findings and sputum was collected; the specimen was acid-fast and culture negative. The patient began treatment with rifampin, isoniazid, pyrazinamide, and ethambutol for 2 months. Six months after initiating this treatment, the patient's condition improved (reduction in local signs of inflammation), but she continued to develop subcutaneous abscesses in the forearm. TB treatment with rifampicin and isoniazid was extended to beyond the expected duration of 6 months, because the abscess specimens continued to grow *M. tuberculosis* on culture despite its susceptibility to the prescribed treatment. The left knee improved completely with treatment. After eight months of TB treatment, a surgical fistulectomy of the right forearm and hand was performed (**Figure 2C and Figure 2D**). This approach was successful and cured the fluid collection and skin lesions completely. The treatment was discontinued after 12 months, when the patient was considered to be cured. The lesion had regressed, but the sequelae were observed in the right thumb (**Figure 2E**). There were no serious adverse effects due to the treatment; graft function remained stable and the blood creatinine level at the end of treatment was 1.6mg/dL. All protocols involving this patient were approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was also obtained from the patient.

DISCUSSION

Herein, we report a case of cutaneous TB with signs and symptoms that began 7 months after kidney transplantation. TB was diagnosed on the basis of suggestive skin biopsy findings and positive culture of synovial fluid from the left knee. The patient was treated with specific anti-TB drugs for 1 year; the infection subsided, but the patient continued to exhibit sequelae in the thumb of her right hand. TB in patients receiving SOTs can be serious, especially owing to the difficulties in making a precise diagnosis. Extra-pulmonary diseases are usually paucibacillary, and acid-fast smears usually do not contribute to the diagnosis. Relying on automatized culture is the best option, but it usually takes time and may not be available. In developing countries, such as Brazil, pulmonary TB is much more common than extra-pulmonary TB, especially the cutaneous form of the disease⁴⁻⁶. The clinical presentation of cutaneous/subcutaneous TB is quite varied and includes inflammatory papules, verrucous plaques, suppurative nodules, and chronic ulcers⁷. In this case,

the lesions started out as violaceous papules, suppurative nodules, and chronic ulcers. The diagnosis was based on skin biopsy findings and culture of the synovial fluid from the left knee of the patient. TB abscesses typically affect malnourished children and immunocompromised adults, including patients receiving SOTs and are rarely reported in immunocompetent patients⁷. The detection of bacilli in cutaneous lesions is a true challenge: on average, all diagnostic methods have lower sensitivity and specificity rates compared to those observed in the pulmonary form of the disease⁸. Histopathological examination is essential to establishing a diagnosis. In this report, a skin biopsy of an ulcer from the right forearm was obtained. It exhibited exudative and chronic inflammation, along with granulomatous areas with giant cells and necrotic areas. Cultures for bacteria, mycobacteria, and fungus yielded negative results. Almost all clinical presentations of TB have a similar histological basis, which includes histiocytes and giant cells, and the histological differences in each patient result from the host's ability to organize the granulomatous processes⁸. When confronted with the possible diagnosis of cutaneous TB, a chest radiograph should always be ordered, as it is sometimes possible to detect active pulmonary TB in these patients. Investigation that comprises obtaining a previous history of exposure to other TB patients and a TST are mandatory. This patient received a transplant, and she did not undergo a TST. Her chest radiograph showed normal findings, and her mother had pulmonary TB 22 years ago. In transplant recipients and dialytic patients, it is not uncommon to witness febrile systemic disease and extra-pulmonary manifestations. Thus, disseminated TB might be one of the clinical presentations observed in these patients, and it may initially present as a fever of unknown etiology. The unusual and varied presentations of TB may cause delays in diagnosis and treatment, as reported in the present case. Many reports claim that latent TB treatment with isoniazid for chemoprophylaxis during dialysis is effective in post-transplant patients with a positive TST test^{9,10}. Nonetheless, a thorough medical history must be obtained from the family and the patient, and patients on dialysis should be submitted to a TST or an interferon-gamma release assay, if possible⁸. Most experts agree that the primary therapy for latent TB should include isoniazid for 6 to 9 months^{1,11,12}.

In conclusion, *M. tuberculosis* infection should always be considered in the differential diagnosis of cutaneous ulcers and nodules in transplant recipients. The active investigation and treatment of latent TB before transplantation may prevent the reactivation of this disease.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial support

Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FAEPA).

REFERENCES

1. Ministério da Saúde. Boletim Epidemiológico. O controle da tuberculose no Brasil: avanços, inovações e desafios. Secretaria de Vigilância em Saúde. 2014;44(2):1-13.
2. Subramanian A, Dorman S. *Mycobacterium tuberculosis* in solid organ transplant recipients. Am J Transpl. 2009;9(suppl4):S57-62.
3. Muñoz P, Rodrigues C, Bouza E. *Mycobacterium tuberculosis* infection in recipients of solid organ transplants. Clin Infect Dis. 2005;40(4):581-7.
4. Matuck TA, Brasil P, Alvarenga MFAC, Morgado L, Reis MD, da Costa ACP, et al. Tuberculosis in renal transplants in Rio de Janeiro. Transpl Proc. 2004;36(4):905-6.
5. Guida JPS, Rosane DB, Urbini-Santos C, Alves-Filho G, Resende MR, Mazzali M. Tuberculosis in renal transplant recipients: a Brazilian center registry. Transpl Proc. 2009;41(3):883-4.
6. Marques ID, Azevedo LS, Pierrotti LC, Caires RA, Sato VA, Carmo LP, et al. Clinical features and outcomes of tuberculosis in kidney transplant recipients in Brazil: a report of the last decade. Clin Transplant. 2013;27(2):E169-76.
7. Santos JB, Oliveira MH, Figueiredo AR, Silva PG, Ferraz CE, Medeiros VLS. Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects - Part I. An Bras Dermatol. 2014;89(2):219-29.
8. Santos JB, Oliveira MH, Figueiredo AR, Silva PG, Ferraz CE, Medeiros VLS. Cutaneous tuberculosis: diagnosis, histopathology and treatment-Part II. An Bras Dermatol. 2014;89(4):545-55.
9. Currie AC, Knight SR, Morris PJ. Tuberculosis in renal transplant recipients: the evidence of prophylaxis. Transplantation. 2010;90(7):695-704.
10. Sidhu A, Verma G, Humar A, Kumar D. Outcome of latent tuberculosis infection in solid organ transplant recipients over a 10-year period. Transplantation. 2014;98(6):671-5.
11. de Lemos AS, Vieira MAMS, Halpern M, Quaresma RG, Borchardt AC, Santos MA, et al. Results of implementation of preventive recommendations for tuberculosis after renal transplantation in an endemic area. Am J Transplant. 2013;13(12):3230-5.
12. Grim AS, Layden JE, Roth P, Gallitano S, Adams W, Clark NM. Latent tuberculosis in kidney and liver transplant patients: a review of treatment practices and outcomes. Transpl Infect Dis. 2015;17(5):768-77.