A Rare Manifestation of Tuberculosis in a Renal Transplant Patient: A Case Report

I.D. Coelho[a,*], C. Romãozinho[b], A.C. Teixeira[c], L. Rodrigues[b], E. Ferreira[c], L. Santos[b], F. Macário[b], R. Alves[b], and A. Figueiredo[d]

[a]Nephrology Department, Amato Lusitano Hospital, Castelo Branco, Portugal; [b]Nephrology Department, Coimbra University Hospital Center, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal; [c]Nephrology Department, Coimbra University Hospital Center, Coimbra, Portugal; and [d]Urology and Kidney Transplantation Department, Coimbra University Hospital Center, Faculty of Medicine of the University of Coimbra, Coimbra, Portugal

ABSTRACT

Cutaneous lesions in the presence of fever in patients undergoing immunosuppressive therapy are a diagnostic challenge and may represent manifestations of multiple diseases, such as fungal infections, nocardiosis, lymphoproliferative diseases, zoonosis, and tuberculosis. The authors report a case of a 66-year-old white man with chronic kidney disease since 2014 (chronic pyelonephritis) who had a renal transplant in the previous 6 months. Induction therapy was performed with thymoglobulin, and his current immunosuppression scheme included tacrolimus, mycophenolate mofetil, and prednisolone. The patient had no history of pulmonary tuberculosis. The patient presented with 2 cutaneous lesions, localized on the back and abdomen, that appeared to be firm, painful, subcutaneous, erythematous nodules with an approximately 5 cm diameter overlying an infected focus and purulent material inside. The patient also had a fever and fatigue. Blood analysis showed pancytopenia with an elevation of inflammatory markers and graft dysfunction. Tissue cultures and skin biopsy with histological analysis were performed. Histopathology of the lesion showed a nonspecific inflammatory infiltrate without granulomas, and acid-fast bacillus staining was negative. Nevertheless, serum QuantiFERON testing was positive. But polymerase chain reaction finally confirmed the presence of *Mycobacterium tuberculosis*, which confirmed the diagnosis of cutaneous tuberculosis. A chest computed tomography scan showed a lung pattern of miliary tuberculosis. The patient was treated with multidrug tuberculosis therapy, resulting in lesion clearance after 3 weeks. Tuberculosis is a serious infection, especially in high-risk patients, such as those in an immunocompromised state. The incidence of cutaneous tuberculosis is rare, but it should be considered in patients presenting with atypical skin lesions suggestive of an underlying infectious etiology.

TRANSPLANTATION is the preferred method of renal replacement therapy in terms of patient survival, quality of life, and cost. Infection is the second cause of death, after cardiovascular disease, in renal allograft recipients. The risk of infection depends on the recipient's state of immunosuppression, epidemiologic exposures, and invasive procedures [1].

The incidence of tuberculosis (TB) in Portugal is approximately 20 cases per 100,000 habitants [2]. Pulmonary disease is the most frequent presentation. However, in patients who have received solid organ transplants, the presentation of TB is a diagnostic challenge because one-third to a half of TB cases occur as extrapulmonary disease [3]. These unusual clinical presentations sometimes delay the diagnosis and treatment [4].

*Address correspondence to Inês Dionísio Coelho, Nephrology Department, Amato Lusitano Hospital, Avenida Pedro Álvares Cabral, 6000-085 Castelo Branco, Portugal. Tel: (+351) 272 000 232; Fax: (+351) 272 000 269. E-mail: dcoelho.ines@gmail.com

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Skin involvement can result from an exogenous or endogenous physiopathologic process. Endogenous invasion is usually due to spread of pulmonary tuberculosis by hematogenous or lymphatic dissemination. Exogenous invasion is due to direct inoculation of bacteria [5].

We present a clinical case of a kidney transplant recipient who presented with cutaneous TB and a lung pattern of miliary tuberculosis 6 months after transplantation.

CASE REPORT

A 66-year-old, white man received a renal transplant from a deceased donor in November 2017 owing to chronic kidney disease (chronic pyelonephritis). Before the transplantation, he was on hemodialysis since 2014. The patient received thymoglobulin to induce immunosuppression, and the current immunosuppression scheme included tacrolimus, mycophenolate mofetil, and prednisolone. The patient had no personal or family history of pulmonary tuberculosis. Six months after surgery, he presented to the emergency department with 2 cutaneous lesions, localized on his back and abdomen, that appeared to be firm, painful, subcutaneous, erythematous nodules with an approximately 5 cm diameter overlying an infected focus and purulent material inside (Fig 1). The patient also had a fever, fatigue, anorexia, and an occasional nonproductive cough. On physical examination, vital signs were within normal limits, the skin demonstrated no other significant changes, and the patient had no notable lymphadenopathy.

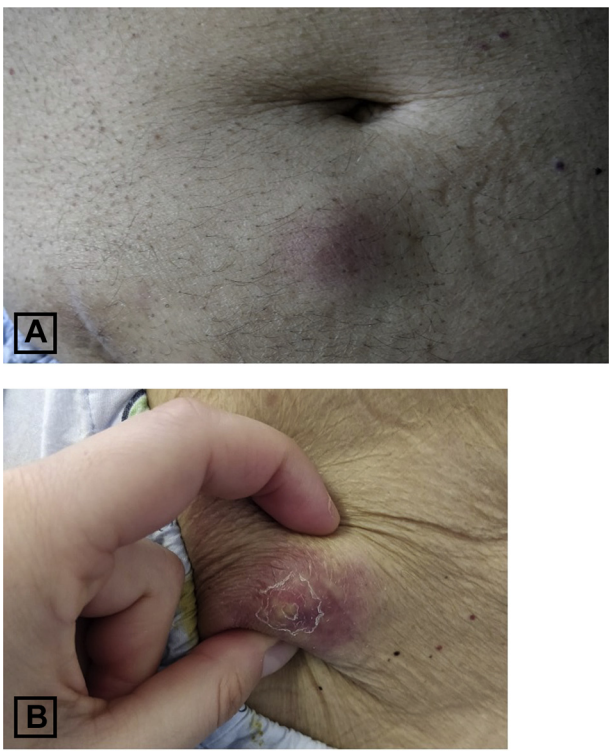

Fig 1. **(A)** and **(B)**: Two cutaneous lesions, located on the back and abdomen. Both are firm, painful, subcutaneous, erythematous nodules with a 5 cm diameter. **(B)** The dorsal lesion had purulent material inside.

Blood analysis showed pancytopenia with an elevation of inflammatory markers and graft dysfunction. We performed tissue cultures and skin biopsy with histological analysis. The patient scored positive with the QuantiFERON-TB Gold test (QFT-Plus; Qiagen) (interferon gamma values of 8.87 IU/mL and 8.97 IU/mL for *Mycobacterium tuberculosis*-specific antigen and mitogen, respectively), raising the suspicion of a TB infection. Histopathology of the lesion showed a nonspecific inflammatory infiltrate, without granulomas, and acid-fast bacillus staining was negative, but polymerase chain reaction (PCR) confirmed the presence of *M tuberculosis*, which confirmed the diagnosis of cutaneous tuberculosis (Fig 2). The isolated *M tuberculosis* was later found to be susceptible to all the first-line antimycobacterial drugs. The patient was transferred to the infectious diseases unit and hospitalized in respiratory isolation. Further investigation with a chest computed tomography scan (Fig 3) showed multiple lung micronodules in all lung fields. There was also thickening of the interlobular septa, particularly evident in the lower right lobe. The distribution of the micronodulation seemed to be of the random type, suggesting a miliary tuberculosis lung pattern. Microbiological examination (acid-fast bacillus staining, culture, and genome detection) for

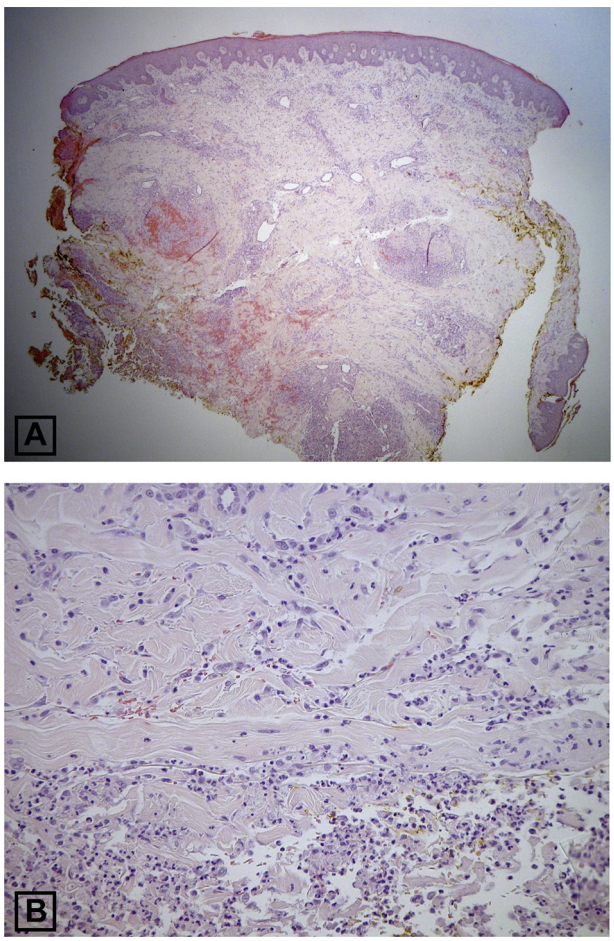

Fig 2. **(A)** Diffuse, superficial and deep, dermal, nonspecific inflammatory infiltrates, without granulomas. (hematoxylin and eosin, ×40). **(B)** Inflammatory infiltrate with neutrophils, histiocytes, and some Langerhans-type, multinucleated giant cells (hematoxylin and eosin, ×200).

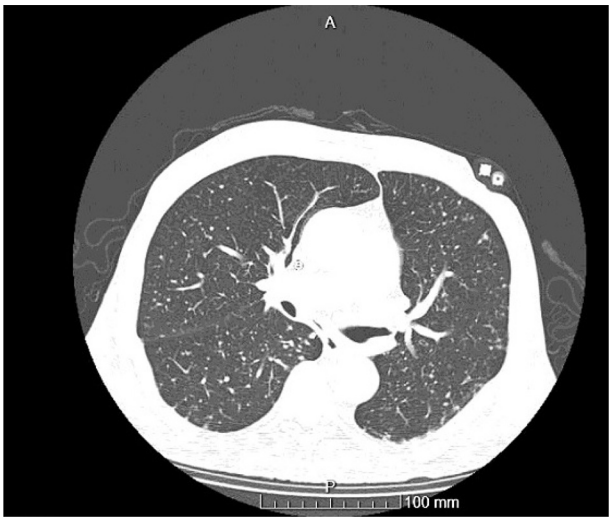

Fig 3. Chest computed tomography scan shows multiple lung micronodules in all lung fields. There is also thickening of interlobular septa, particularly evident in the lower right lobe. The distribution of the micronodulation seems to be of the random type, suggesting the diagnosis of miliary tuberculosis.

mycobacteria was conducted also on urine, blood, and bronchoalveolar lavage with positive results.

The patient was treated with a multidrug TB therapy (pyrazinamide, rifampin, ethambutol, and isoniazid) in doses adjusted to the renal function, resulting in cutaneous lesion clearance after 3 weeks. The immunosuppressive therapeutic was adjusted, given the state of severe immunosuppression of the patient. However, the patient suffered progressive worsening of graft function, with an extended hospitalization marked by a pancytopenia of very difficult resolution. Finally, the patient developed graft failure and returned to the hemodialysis. During all the course of the disease, pulmonary symptoms were always mild (occasional nonproductive cough) and resolved after the beginning of TB therapy.

DISCUSSION

We report a case of cutaneous TB with signs and symptoms that began 6 months after kidney transplantation. TB was diagnosed on the basis of suggestive skin biopsy findings and confirmation of the presence of *M tuberculosis* by DNA PCR on the skin biopsy specimen. In fact, DNA PCR should be considered in preference over culture for the diagnosis of cutaneous TB with inconclusive histopathology [6] because it represents the most effective and rapid tool to make a diagnosis. In our patient, DNA PCR on the skin biopsy specimen was crucial because histopathology did not have the typical granuloma formation seen on TB cases, which may occur in immunocompromised patients.

The clinical presentation of cutaneous and subcutaneous TB is quite varied and includes inflammatory papules, verrucous plaques, suppurative nodules, and chronic ulcers [7]. In this case, the cutaneous lesions were localized on the back and abdomen, appeared as firm, painful, subcutaneous, erythematous nodules, and had an approximately 5 cm diameter overlying an infected focus and purulent material inside.

Additionally, the patient had a miliary tuberculosis lung pattern. Cutaneous manifestations of miliary tuberculosis are extremely rare and produced by the hematogenous dissemination of *M tuberculosis* to the skin in immunocompromised patients. In our patient, it was possible to isolate *M tuberculosis* in a blood specimen, which is not common. The cutaneous lesions in patients with miliary tuberculosis can appear on the trunk and have erythematous papulovesicular features [8], but other authors describe that cutaneous manifestations of miliary tuberculosis are nonspecific [9].

TB in patients receiving solid organ transplants can be a serious condition, impacting graft and patient survival, as this case report emphasizes. The precise diagnosis is difficult to obtain since extrapulmonary diseases are usually paucibacillary, acid-fast stain does not contribute to the diagnosis, and there is a nonuniform distribution of the bacteria [10].

CONCLUSION

This case emphasizes a rare cutaneous manifestation with a hematogenous dissemination of *M tuberculosis* that can develop in immunocompromised patients. Despite the severity of pulmonary involvement with a miliary tuberculosis lung pattern, the patient had only mild respiratory symptoms, and this diagnosis was made after the rare presentation of cutaneous tuberculosis. *M tuberculosis* infection should always be considered in the differential diagnosis of atypical skin lesions suggestive of an underlying infectious etiology.

REFERENCES

[1] Veroux M, Giuffrida G, Corona D, Gagliano M, Scriffignano V, Vizcarra D, et al. Infective complications in renal allograft recipients: epidemiology and outcome. Transplant Proc 2008;40:1873–6.

[2] Tuberculose em Portugal. Desafios e Estratégia. Direcção Geral da Saúde, www.dgs.pt; 2018 [accessed 12.09.18].

[3] Moyses-Neto M, Drumond D, Morgantetti G, Garcia TMP, Bolella VR, Romao EA. Cutaneous and articular tuberculosis in a renal transplant recipient. Rev Soc Bras Med Trop 2017;50:565–7.

[4] Subramanian A, Dorman S. *Mycobacterium tuberculosis* in solid organ transplant recipients. Am J Transplant 2009;9(Suppl. 4):S57–62.

[5] Hill MK, Sanders CV. Cutaneous tuberculosis. Microbiol Spectr 2017;5. https://doi.org/10.1128/microbiolspec.TNMI7-0010-2016.

[6] Agarwal P, Singh EN, Agarwal US, Meena R, Purohit S, Kumar S. The role of DNA polymerase chain reaction, culture and histopathology in the diagnosis of cutaneous tuberculosis. Int J Dermatol 2017;56:1119–24.

[7] Santos JB, Figueiredo AR, Ferraz CE, Oliveira MH, Silva PG, Medeiros VL. Cutaneous tuberculosis: epidemiologic, ethiopathogenic and clinical aspects - part I. An Bras Dermatol 2014;89:219–28.

[8] De Maio F, Trecarichi EM, Visconti E, Sanguinetti M, Delogu G, Sali M. Understanding cutaneous tuberculosis: two clinical cases. JMM Case Rep 2016;3:e005070.

[9] Suraprasit P, Silpa-archa N, Triwongwaranat D. Cutaneous miliary tuberculosis in a chronic kidney disease patient. Case Rep Dermatol 2014;6:253–7.

[10] Mehta PK, Raj A, Singh N, Khuller GK. Diagnosis of extrapulmonary tuberculosis by PCR. FEMS Immunol Med Microbiol 2012;66:20–36.