Case Report: Leprosy and Tuberculosis Co-Infection: Clinical and Immunological Report of Two Cases and Review of the Literature

Maria Ângela B. Trindade, Denise Miyamoto, Gil Benard,* Neusa Y. Sakai-Valente,
Dewton de M. Vasconcelos, and Bernard Naafs

Hanseniasis Outpatient Unit, Laboratory of Medical Investigation Units 56 and 53, Division of Dermatology, Clinics Hospital, Medical School, University of São Paulo, Brazil; Health Institute, São Paulo State Health Department, Brazil; Laboratory of Medical Mycology, Tropical Medicine Institute, University of São Paulo, Brazil; Stichting Tropen Dermatologie Munnekeburen, The Netherlands

Abstract. A review of the records of patients seen between 2004 and 2011 at the Dermatology Clinic of the São Paulo University Medical School showed that only two leprosy patients had been co-infected with tuberculosis (TB). One patient showed a type 1 leprosy reaction during the first 3 months of treatment of pleural TB and in the other patient, pulmonary TB was diagnosed during the first 3 months of treatment of a type 1 leprosy reaction. Both patients showed normal cellular immune response tests, including those of the interferon-gamma (IFN- γ)/interleukin 12 (IL-12) axis. Although both mycobacterial infections are endemic in developing countries like Brazil, the co-infection has hardly been reported in the last decade. There is no suitable explanation for this observation. The reports on the interaction between the two mycobacteria are highly speculative: some studies suggest that leprosy, especially the anergic form, would predispose to TB, whereas other investigations suggested an antagonism between the two diseases.

INTRODUCTION

There are still more than 200,000 new cases of leprosy and more than 9 million new cases of tuberculosis (TB) registered annually worldwide,^{1,2} despite improvements in treatment and living conditions. Presently, leprosy is particularly prevalent in clusters in developing countries, such as in the north, the northeast, and the central west of Brazil with more than 30,000 new cases per year.³ Incidence of TB has been increasing because of the human immunodeficiency virus (HIV) pandemics and the growing number of patients under medical immune-suppression. More than 70,000 new cases of TB are annually reported in Brazil.⁴

Both diseases are chronic granulomatous infections caused by intracellular Gram-positive aerobic acid-fast bacilli that multiply slowly and have long incubation periods. According to Lázaro and others,⁵ about 5% of the *Mycobacterium leprae*-infected individuals in endemic areas are predisposed to leprosy. A similar figure holds for TB: more than 90% of the infected individuals will not develop the disease.⁶ There are multiple presentations of both diseases depending on the host's cell-mediated immune response. The spectrum of TB comprises at one pole the anergic, multibacillary forms like the miliary and periorificial forms and, at the other pole, the hyperergic, paucibacillary forms like lupus vulgaris and verrucous TB; "id" reactions such as the papule-necrotic tuberculoid and erythema induratum of Bazin are also relevant presentations of TB.⁷

In leprosy, a similar polarity is observed: paucibacillary tuberculoid leprosy (TT), with a predominant cell-mediated immune response, multibacillary lepromatous leprosy (LL), with a predominant humoral immune response, and between the poles, the intermediate borderline forms: borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL).⁸ The disease is chronic, but about 40–50% of the borderline patients will experience acute reactions, with exacerbation of cellular immune response (type 1 reaction) or humoral

immune response (type 2 reaction) at some time during the course of treatment. Nevertheless, reactions are part of the normal course of the disease and may therefore also occur in patients without treatment.⁹

We hereby report two patients with leprosy and TB co-infection, an association that is rarely reported at present, even in areas where both diseases are endemic. We discuss possible reasons for this phenomenon, and the interplay between these two infections, a matter not yet clear, and review the literature on this coinfection.

CASE 1

A 31-year-old Afro-Brazilian man was referred to us for parasthetic skin lesions he had for 3 months. Six months before he had sought medical care as a result of a 6-week history of fever, night sweats, weight loss, and asthenia. Chest x-ray revealed a pleural effusion (Figure 1A). Pleural fluid examination showed an exudate with 2,200 cells/mm³ of predominant (90%) lymphocytes and highly elevated adenosine deaminase (129.6 U/mL, normal range up to 2 U/mL). A tuberculin skin test was positive with a 14 mm induration. Pleural TB was then diagnosed and Brazilian standard multidrug therapy (rifampicin, isoniazid, and pyrazinamide) was started. Two weeks later symptoms had subsided and the patient started to gain weight. Radiological evolution at 2 months showed complete resolution of the pleural effusion, with a remaining discrete pleural thickening (Figure 1B). He had completed 4 months of therapy when first seen at our service. At skin inspection, multiple erythematous hypo-anesthetic papules and nodules, single and confluent, forming edematous infiltrated plaques on the trunk, face, hand palms, and soles were seen (Figure 1C and D). The left ulnar nerve was thickened, earlobes were infiltrated, and there was bilateral conjunctival hyperemia. Histopathology of the earlobes showed dermal edema and granulomas with epithelioid histiocytes, a few multinucleate giant cells, and lymphocytes surrounding blood vessels, appendages, and nerves. Fite-Faraco staining showed granular acid-fast bacilli (2+/6+) in macrophages and nerves (Figure 2A). Immunohistochemistry with anti-Bacillus Calmette-Guérin (BCG) antibody confirmed the presence of mycobacterial antigenic determinants inside the nerves. A BB-BT leprosy in mild leprosy

*Address correspondence to Gil Benard, Laboratory of Medical Investigation Unit 56, Division of Clinical Dermatology, Medical School, University of São Paulo, Av Dr Eneas de Carvalho Aguiar 470, CEP 05403-000, São Paulo, Brazil. E-mail: mahong@usp.br

FIGURE 1. Patient 1: Chest x-rays showing the left pleural effusion before (A) and its complete resolution after 2 months of anti-tuberculosis treatment (B). Erythematous edematous hypoesthetic plaques and papules on the trunk (C) and face (D).

type 1 reaction was diagnosed and multidrug therapy (MDT-MB: rifampicin, clofazimine, and dapson) was prescribed for 1 year. A non-hormonal anti-inflammatory drug was also prescribed occasionally. The patient responded well and after 2 years he had no skin or lung lesions or disabilities.

CASE 2

A 46-year-old Caucasian woman complained of red macules on the face and on the right foot for one year. Dermatological examination showed erythematous papules on the right forearm, erythematous hypo-anesthetic plaques with ill-defined margins on the left knee, and two hypoesthetic erythematous, edematous-infiltrated plaques on the face and

right foot (Figure 3A and B). Histopathology from the lesion on the face showed granulomas consisting of epithelioid histiocytes and lymphocytes, with central caseous or fibrinoid necrosis, surrounding appendages, vessels, and nerves; there was no staining for acid-fast bacilli with Fite-Faraco. Immunohistochemistry with anti-BCG antibody showed *Mycobacterium* antigenic determinants inside nerves (Figure 2B and C). Mitsuda reaction was positive (6 mm) and histology showed a tuberculoid granuloma. The tuberculin skin test was 10 mm in diameter. Taking the clinical and histopathological findings into account, she was diagnosed as BT-BB leprosy in a type 1 leprosy reaction. She was prescribed MDT-MB and prednisone (0.5 mg/kg/day). After 1 month of treatment, she presented with dyspnea, palpitation, and weight loss. High-resolution

FIGURE 2. (A) Fite-Faraco staining of a biopsy of patient 1 showing granular bacilli within histiocytes and nerves ($\times 400$); (B) anti-Bacillus Calmette-Guérin (BCG) immunohistochemistry ($\times 400$) of a skin biopsy of patient 2 showing intense positive acid-fast bacilli inside nerve (brown). (C) Immunohistochemistry with anti-BCG (brown) and S-100 protein (red, used as a marker for Schwann cells) of a skin biopsy showing acid-fast bacilli within nerves ($\times 1000$).

FIGURE 3. Patient 2: Erythematous edematous plaques and papules on (A) the left malar region, nose, glabella, and front and (B) the right foot. High-resolution computed tomography scan at the level of the upper lobes showing (C) retracted parenchymal opacification and pleural thickening and (D) reticulation, parenchymal opacification, and ground glass opacities associated with traction bronchiectasis.

computed tomography showed bi-apical irregular and ground-glass opacities and branching linear structures (Figure 3C and D). One of three sputum sample cultures was positive for *Mycobacterium tuberculosis*. She was then followed at a TB service where she started multidrug therapy with rifampicin, isoniazid, and pyrazinamide. After 6 months her pulmonary TB had resolved but she was readmitted at our service because of worsening of the erythema and edema of the plaques on her face and the right foot, pointing again to a type 1 reaction. During the TB treatment she was lost from our follow-up and did not take the MDT-MB drugs. Treatment was restarted in association with low-dose prednisone (10 mg/day), for additional 12 months. However, because at that time a low hemoglobin level and glucose 6-phosphate deficiency were diagnosed, dapsone was omitted from the regimen. At the end of the leprosy treatment she persisted with erythema and paraesthesia on the face, minimal signs of type 1 reaction that subsequently improved with low-dose, long-term prednisone. One year later, she had no skin or lung complaints or disabilities except for hypoesthesia of the scar on the right foot.

IMMUNOLOGICAL EVALUATION

Susceptibility to mycobacterial infections may be linked to cellular immune defects, especially of the Th-1 cytokine cascade.¹⁰ Thus, the dual mycobacterial infection led us to inves-

tigate the cellular immune functions of the patients. Both patients showed normal TCD4+, TCD8+, B-cell, and natural killer peripheral blood cell counts. The expression of the beta-1 chain of the interleukin-12/23 (IL-12/23) receptor (CD212) and alpha chain of the IFN-gamma (IFN- γ) receptor (CD119) were also normal. The lymphocyte proliferative response to non-specific stimuli such as the phytohemagglutinin and pokeweed mitogen and the anti-CD3 antibody were also within normal limits in both patients. Lymphocyte proliferative responses to tetanus toxoid and a *Candida* metabolic antigen were below the normal range of the laboratory (stimulation index [SI] ≥ 3.0), but normal (SI > 3.0) to *M. tuberculosis* purified protein derivative (PPD-T, Statens Serum Institute, Copenhagen, Denmark). Thus, no major defect in the Th-1 arm of the cellular immune response could be detected in the two patients with this set of tests.

DISCUSSION

The interaction between leprosy and TB and its repercussions on the incidence of each other still remain a matter of debate.¹¹ Interestingly, many case reports and cohorts studies have been published from the 50s up to the mid-80s reporting the frequent association between TB and leprosy in areas where both diseases were endemic,¹²⁻¹⁷ but rarely thereafter.

In addition, *postmortem* studies had previously documented the high incidence of TB as the cause of death in leprosy patients.^{18,19} Overall, these studies suggested that leprosy, especially the anergic form, predispose to TB.

In fact, the interaction between both diseases dates from ancient times. Donoghue and others²⁰ demonstrated the presence of disseminated *M. leprae* and *M. tuberculosis* co-infection in human archaeological samples dating from the Roman period using polymerase chain reaction. They argued that the impaired cell-mediated response to *M. leprae* of lepromatous leprosy patients would favor the advance of the more virulent pathogen *M. tuberculosis*. This is in contrast with other early investigations that suggested an antagonism between the two diseases, i.e., that those individuals with acquired immunity against *M. leprosy* would be less susceptible to pulmonary TB than the general population because of cross-immunity; the reverse would depend on the immune status of the patient, i.e., the hyperergic ("allergic"), but not the anergic form of leprosy, would be protective.²¹ Since then authors have either agreed or disagreed with this hypothesis.^{13,15–17,22–24} Experimental evidence gives support to the existence of cross-protection among these mycobacteria.²⁵

Despite this long debate, the issue of the interaction between the two epidemics still remains to be clarified. This debate apparently ceased to be fueled because of the yet unexplained recent decline in the number of reports of co-infected patients. Only a few other co-infection cases have been reported more recently in the literature^{11,26–31}; of note is the lack of reports on this association in Brazil, where both diseases are endemic. The present two cases are the only co-infected patients registered in our service during the 2004–2011 period. Currently, there is not a suitable explanation for this observation, as discussed below. Nonetheless, this issue still carries a serious consequence, represented by the risk that a leprosy treatment becomes a TB "monotherapy" (with clofazimine, because rifampicin is used only once monthly) when the diagnosis of the latter is missed.

It has also been suggested that TB is more severe in co-infected patients¹⁷; however, this was not the case in our patients. Patient 1 presented a benign form of TB, pleural TB. He was on TB treatment when he presented skin lesions of type 1 leprosy reaction. Thus, in a similar fashion to the concept that the reaction that occurs in HIV-leprosy co-infected patients receiving high activity antiretroviral treatment would represent a manifestation of their immune-recovery,³² the TB treatment may have had an upgrading immunological effect caused by the release of antigens by *M. leprae* organisms killed by the rifampin present in the TB treatment or because of an immune recovery caused by healing of the TB. The second patient had mild pulmonary TB that presented during prednisolone treatment of a type 1 leprosy reaction during MDT. Her leprosy, BT, also tended to the more benign pole of the disease. This patient probably had better immunity to both *Mycobacteria* species than patient 1, but her immunity may have been decreased because of the corticosteroids necessary to treat the leprosy reaction, hence the occurrence of TB. Moreover, the second episode of type 1 reaction that she developed with TB treatment also was probably associated with the therapeutic effect of rifampicin.

An important finding is the normal result of the cellular immune response tests, including the investigations regarding

the IFN- γ /IL-12 axis, which drives effective Th-1 responses. Recently, a case of triple infection, leprosy, TB, and leishmaniasis, in which all three diseases assumed the "anergic" form, led the investigators to assess genetic defects in the T-helper 1 arm of the immune response. Although the patient showed some degree of IL-12 unresponsiveness, no genetic defect could be detected³³; this issue is of interest, once deficiencies in the IFN- γ /IL-12 axis are among the commonest defects leading to genetic susceptibility to mycobacterial diseases.¹⁰

The prevalence of TB and leprosy persists rather high in endemic areas^{1,2}; it is of note that the association between both diseases is declining in most leprosy highly endemic countries, although it seems to be very rarely registered in Brazil. A co-infection with two pathogens that seem to depend on similar defense mechanisms should be much more common. One such example is the more prevalent association of TB and paracoccidioidomycosis, a chronic granulomatous fungal infection common in Brazil: 5–10% of the patients with the mycosis have concomitant pulmonary TB.³⁴ One possible explanation for the decrease in the reports of co-infected cases is BCG vaccination, which has shown to provide at least some partial protection against both diseases.^{35,36} The decrease in the detection rate of leprosy in Brazil was indeed significantly correlated with the increase in BCG coverage.³⁷ Furthermore, we hypothesize that in other leprosy highly endemic countries like India and French Polynesia the improvement in BCG coverage,^{38,39} although still partial, may also have had the same effect.

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Authors' addresses: Maria Ângela B. Trindade, Division of Clinical Dermatology, Clinics Hospital, Medical School, University of Sao Paulo, Brazil and Health Institute, São Paulo State Health Department, Brazil, E-mail: angelatrindade@uol.com.br. Denise Miyamoto, Division of Clinical Dermatology, Clinics Hospital, Medical School, University of Sao Paulo, Brazil, E-mail: dmiyamoto@gmail.com. Gil Benard, Laboratory of Medical Investigation Unit 56, Division of Clinical Dermatology, Medical School, University of Sao Paulo, Brazil and Laboratory of Medical Investigation Unit 53, Tropical Medicine Institute, University of São Paulo, Brazil, E-mail: mahong@usp.br. Neusa Y. Sakai-Valente, Laboratory of Medical Investigation Unit 53, Tropical Medicine Institute, University of São Paulo, Brazil, E-mail: neusavalente@telefonica.com.br. Dewton de M. Vasconcelos, Laboratory of Medical Investigation Unit 56, Division of Dermatology, Clinics Hospital, Medical School, University of Sao Paulo, Brazil, E-mail: dmvascon@usp.br. Bernard Naafs, Stichting Tropen Dermatologie Munnekeburen, The Netherlands, E-mail: bennaafs@dds.nl.

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