Case Report: A Patient with Erythema Nodosus Leprosum and Chagas Cardiopathy: Challenges in Patient Management and Review of the Literature

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Abstract. We report a patient with severe multi-bacillary leprosy complicated by recurrent episodes of erythema nodosum necroticans that required thalidomide and/or corticosteroids during follow-up. Although the patient was from an area to which Chagas disease is endemic, this diagnosis was initially missed and was only investigated when heart failure developed in the patient. The difficulties of managing erythema nodosum necroticans and heart failure concomitantly and those involved in excluding the diagnosis of acute myocarditis caused by reactivation of Chagas disease secondary to the immunosuppressive regimen are discussed. Other potential causes for the heart failure and possible interactions between the two diseases and their treatments are discussed. We also reviewed the literature for the association between leprosy and Chagas disease, both of which are highly endemic in Brazil. This case emphasizes the importance of searching for subclinical co-infections in leprosy patients because reactions frequently develop during specific treatment in these patients, and these reactions require prolonged therapy with immunosuppressive drugs.

INTRODUCTION

Leprosy and Chagas disease are chronic infections that are endemic to several parts of the world. Despite the efforts that have been put forward by public health institutions and the World Health Organization towards their control, more than 200,000 new leprosy cases are reported worldwide each year, and approximately eight million persons in Latin America have Chagas disease.^{1,2} Although Chagas disease has been controlled in several disease-endemic areas, leprosy persists as a challenging endemic disease, as shown by active transmission in several countries worldwide, including Brazil.^{1,3} These diseases present insidious onsets with clinical symptoms that appear a long time after the primary infection, and therefore are often diagnosed and treated at advanced stages, leading to severe disabilities and even death.

Leprosy is a granulomatous disease caused by *Mycobacterium leprae* that involves nerves and skin. Because of variations in host immune responses, a spectrum of different clinical, bacteriologic, and histologic manifestations is reported. In the hyperergic tuberculoid pole, the patients have strong cell-mediated immune responses, whereas in the anergic lepromatous pole, humoral immune responses predominate.⁴ Between these polar forms are the borderline patients, who may have variable degrees of specific cellular immune response.⁵ Patients at the lepromatous pole may undergo episodes of acute reaction because of flareups of their immune responses, usually during specific treatment. These reactions are characterized by abrupt eruption of erythematous and painful nodules, usually on skin, but may involve any organ or tissue infected by bacilli, and systemic manifestations, known as erythema nodosum leprosum (ENL). Erythema nodosum leprosum in its

more severe form can evolve into necrosis and ulcerations (erythema nodosum necroticans [ENN]). It is usually associated with an exacerbated humoral immune response, although cellular immune mechanisms are also present with high tumor necrosis factor- α and interleukin-6 (IL-6) levels⁶ and is treated with immunosuppressive drugs.

Chagas disease shows a chronic evolution with different clinical outcomes according to the immune reactivity of the patient, thus also manifesting as a spectral disease. Three main clinical forms are recognized: the indeterminate, cardiac and digestive forms. Chagas heart disease will develop in approximately 30% of the patients with chronic infection with *Trypanosoma cruzi*.⁷ It is believed that the cardiac lesions are the result of combined damage produced by the parasitism and by the host immune response, either parasite-driven or as an autoimmune phenomenon.⁸

We report a leprosy patient with repeated episodes of ENN in whom severe heart failure developed during her follow up, but whose diagnosis of Chagas disease was initially missed. We discuss the difficulties in managing a patient with both diseases, review the literature of heart failure in leprosy patients, and discuss the possible interaction between these infections and their treatments.

CASE REPORT

A 56-year-old Afro-Brazilian woman from Minas Gerais, Brazil, a state to which Chagas disease is highly endemic, was admitted to our hospital with a three-month history of disseminated painful lumps. At examination, she had diffuse facial infiltration, madarosis of the eyelashes and eyebrows, and multiple painful erythematous nodules covered by yellow papules on the lower limbs and abdomen. These nodules were associated with thermal hypoesthesia, which were also found on the feet. Leprosy was suspected and confirmed by a skin biopsy of the lesion (numerous intact and granular bacilli by Fite-Faraco staining). Multidrug therapy (MDT) (rifampicin, dapsone, and clofazimine) for multi-bacillary leprosy was prescribed and showed good initial clinical response. Strongyloidiasis and

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ascariasis were also diagnosed and treated. Results of subsequent stool examinations were negative for both parasites.

After three months, although regression of the skin infiltration was noted, the patient had fever, malaise, edema of lower limbs and feet, and necrosis with small ulcerations of the papules. A bilateral ulnar neuritis was also observed. Erythema nodosum necroticans was diagnosed and treated with thalidomide (100 mg/day) and prednisone (0.5 mg/kg/day) for the neuritis. The symptoms subsided in a few days.

Despite this approach, the patient continued to have recurrent episodes of acute ENN with progressive worsening of her general condition. The necrotizing lesions of the lower limbs progressed to larger ulcers, complicated by episodes of cellulitis and worsening of the edema of the legs and feet, which required antibiotic therapy. These episodes were in general partially controlled by periodically increasing the dose of thalidomide to 300 mg/day and that of prednisone to 1 mg/kg/day.

By the eighth month of receiving MDT, she had a new acute episode of ENN. However, at this time, she had dyspnea and anasarca. A diagnosis of class III functional heart failure on the basis of the New York Heart Association classification was made. Examinations showed an increased heart-thorax index by chest radiograph (Figure 1). An electrocardiogram showed anterosuperior divisional block and other abnormalities compatible with Chagas cardiopathy (Figure 2). There was also a decrease of the diastolic end volume and a slight decrease in low ejection fraction by echocardiogram. B-type natriuretic peptide levels were increased. She was then hospitalized and treated for heart failure with diuretics and liquid restriction. Anemia and a mild hypertension were also treated with iron supplementation, folic acid, and an inhibitor of the angiotensin convertase enzyme.

She returned to the outpatient clinic for follow-up of the heart failure and leprosy. Adherence to treatment was poor and after completion of two years of MDT, a new episode of ENL occurred, accompanied by more severe dyspnea and anasarca, which required intensive care unit support for four days. We then investigated the etiology of the heart failure.

Chagas disease was confirmed by positive serologic results for antibodies against *T. cruzi* (indirect immunofluorescent

FIGURE 2. Electrocardiogram for the patient showing an anterosuperior divisional block, a disturbance of right bundle branch conduction, nonspecific alterations of ventricular repolarization of the anterior and septal wall and periods of ectopic atrial rhythm.

assay titer of 1:160 [cutoff titer $\geq$ 1:40; bioMérieux, Marcy L'Étoile, France], an enzyme-linked immunosorbent assay result of 6.1 [cutoff result of 0.4; Ebram, São Paulo, Brazil], and an indirect hemagglutination assay titer of 1:160 [cutoff titer $\geq$ 1:40; bioMérieux, Rio de Janeiro, Brazil]. Direct parasitologic examinations for *T. cruzi* in the blood (leukocyte cream and quantitative buffy coat) were then performed to investigate the possibility of acute myocarditis caused by reactivation of Chagas disease caused by prolonged thalidomide and corticosteroid therapy. Both test results were negative, which together with prompt clinical improvement of the patient without receiving specific therapy against *T. cruzi* therapy, ruled out this diagnosis. Indirect parasitologic enrichment tests (*in vitro* xenodiagnosis and blood culture) showed negative results. A qualitative polymerase chain reaction (PCR) for *T. cruzi* kinetoplast DNA was performed twice with blood samples and showed negative results both times.

The possibility of cutaneous Chagas disease as a cause of erythema nodosum-like lesions was also investigated because reactivations might have occurred in tissues without systemic expression. A new biopsy of a skin lesion was performed but nests of *T. cruzi* amastigotes were not identified.

Histologic examination showed a diffuse neutrophilic inflammatory infiltrate with edema and vacuolated histiocytes, typical of ENN, and granular bacilli by Fite-Faraco staining. Additionally, an immunohistochemical study identified cell phenotypes and cytokine infiltrating the granuloma, but did not identify *T. cruzi* antigens permeating the lesion (Figure 1). The clinical condition of the patient then stabilized, and she was prescribed thalidomide (50 mg/day) and prednisone (10 mg/day) for persistent mildly reactive skin lesions, and antihypertensive drugs. Her heart failure was controlled and the leprosy lesions were considered cured with 24 months of therapy.

DISCUSSION

Leprosy and Chagas disease persist as endemic diseases in Latin America and have a significant effect on local public health. However, they are still considered neglected diseases.⁹ Diagnosis of these infections is frequently delayed even in disease-endemic areas. Chagas disease frequently evolves as a chronic cardiopathy whose prognosis and effect on the quality of life of the patient is highly dependent on early diagnosis

FIGURE 1. Increased heart-thorax index on a chest radiograph of the patient caused by a global cardiomegaly with predominance of left ventricle dilatation.

and treatment. The same characteristics are true for leprosy; in its advanced forms, it can cause permanent disabilities and perpetuate transmission of the disease.¹

We report a patient with a severe multi-bacillary leprosy complicated by recurrent episodes of ENN that required, in addition to the appropriate MDT, thalidomide and/or corticosteroids during her entire follow-up period. Although the patient was from a region to which Chagas disease was endemic, this diagnosis was missed at the beginning of the follow-up. The diagnosis was determined only after cardiac complications developed. She had two acute episodes of heart failure during her follow-up, one severe enough to require intensive care unit support. This complication shows the difficulties in managing a patient with the two diseases, especially when one of the diagnoses has not been suspected.

Association of leprosy and chronic Chagas disease cardiopathy has seldom been reported. Earlier studies showed that 14% of the leprosy patients in a colony in Minas Gerais, Brazil, a state to which both diseases are endemic, had positive serologic test results for Chagas disease.¹⁰ However, detailed studies of Chagas disease manifestations in these patients were not provided. Another study with leprosy patients from the same state showed a higher frequency of seropositive patients (38.6%) for Chagas disease, but the discrete alterations found in electrocardiographic and heart-thorax indices were not different from those in a group of leprosy patients without *T. cruzi* infection.¹¹ The authors suggested that leprosy did not interfere with the course of Chagas disease and *vice versa*. Conversely, they suggested that leprosy can cause cardiovascular alterations, mainly through involvement of the autonomic nervous system, which leads to abnormalities in cardiac electrophysiology. This suggestion was corroborated by the high frequency (45.3%) of leprosy patients with electrocardiographic abnormalities in their study.

Another hypothesis would be direct involvement of the coronary vessels during leprosy.¹² Electrocardiographic alterations were studied in a small series of leprosy patients from Argentina with evidence of *T. cruzi* infection, and electrocardiographic abnormalities were found almost equally in co-infected patients and in the two control groups, leprosy patients who were not infected with *T. cruzi* and *T. cruzi*-infected patients who did not have leprosy.¹³ A more recent report described a Chagas disease patient with lepromatous leprosy whose necropsy demonstrated *Mycobacteria* sp. and *Trypanosoma* sp. inside heart nerve filaments.¹⁴

One of the challenges in management of the patient was to exclude myocarditis caused by reactivation of *T. cruzi* as the cause of the decompensation of the chronic cardiopathy. Reactivation could be caused by either immunosuppression secondary to *M. leprae* infection or to immunosuppressive treatment of the leprosy. Recent data showed that *M. leprae* fractions induce anergy by altering T cell receptor (TCR) and TCR/CD28 signaling events, which resulted in reduced production of IL-2 and inhibition of T cell proliferation, and favored longer intracellular survival of the bacilli.¹⁵ The deficiency of macrophage activation may interfere with the control of *T. cruzi*, enabling increases in parasitemia and further reactivation of Chagas disease.

Conversely, clinical deterioration caused by *T. cruzi* reactivation has been recognized in patients with different immunosuppressive conditions, such as human immunodeficiency virus/acquired immunodeficiency syndrome, transplantation,

and drug-induced immunosuppression. In patients infected with human immunodeficiency virus, reactivation involves mainly the central nervous system, which is followed in frequency by myocarditis.¹⁶ Transplant recipients may show reactivation of Chagas disease, most often after corticosteroid pulse therapy for treating episodes of rejection.^{17,18} In addition to myocarditis and fever and patent parasitemia, reactivation can manifest as cutaneous nodes or panniculitis, mimicking an erythema nodosum.^{18,19} In these cases, nodules with nests of amastigote forms are found.

We performed an additional biopsy of a cutaneous lesion to exclude cutaneous Chagas disease. The presence of a diffuse neutrophilic inflammatory infiltrate and granular bacilli but no amastigotes nests in the biopsy specimen, together with a negative result for the immunohistochemical study of *T. cruzi* antigens, confirmed ENN as the sole etiology of the skin lesions. The criteria for defining reactivated Chagas disease are the clinical manifestations and identification of the parasite by direct microscopy of blood samples such as a buffy coat and/or identification of amastigotes among the inflammatory process in biopsy specimens of the lesions.²⁰ Results of buffy coat examination were negative for parasites, and the absence of parasites in the biopsy specimen of the nodules excluded the diagnosis of cutaneous reactivation of Chagas disease.

Moreover, although Chagas disease myocarditis was initially considered, this diagnosis was excluded on the basis of negative results for parasitologic tests and clinical follow-up. Heart failure in the patient quickly improved after supportive measures but without specific treatment of Chagas disease. Thus, a myocardial biopsy was not necessary. Molecular tools for identifying *T. cruzi*-specific sequences on nuclear or kinetoplast DNA show a better sensitivity compared with parasitologic methods.^{21,22} A qualitative PCR for *T. cruzi* kinetoplast DNA, which amplifies a 330-basepair minicircle sequence, has been standardized in our laboratory according to the protocol of Avila and others.²³ Our preliminary experience with Chagas disease reactivation in patients with acquired immunodeficiency syndrome shows 100% sensitivity for this test (Freitas VL, Shikanai-Yasuda MA, unpublished data). Thus, in our patient, a negative kinetoplast DNA qualitative PCR result in blood reinforced the diagnosis of heart failure associated with chronic, but not reactivated, Chagas disease cardiopathy.²⁴

In our patient, corticosteroids may have aggravated the hypertension and lead to fluid overload usually associated with sodium retention, both of which may have helped to induce heart failure. Additionally, corticosteroids may have a direct action on cardiac function. They can provoke ventricle remodeling, abnormal contractility with fibrosis, hypoxia, oxidative stress and low ventricle function in experimental models.²⁵ These effects are mediated by the angiotensin receptor, which suggests that angiotensin II is involved in the physiopathology of myocardial alterations. This mechanism may have contributed to the decompensation of the cardiac performance of the patient because she had had up to that time an apparently incipient chagasic cardiopathy.

Chagas cardiopathy is characterized by fibrosis, in addition to abnormalities in heart conduction and arrhythmias.²⁶ In addition, corticosteroids also interfere with microbicidal mechanisms of macrophages, either by inhibiting the release of toxic molecules such as nitric oxide, or by altering the Th-1/Th-2 balance.²⁷ Glucocorticoids inhibit the release of IL-12 by macrophages, resulting in the deficiency of interferon- γ

FIGURE 3. Immunophenotypical analysis of infiltrating cells of an erythema nodosum necroticans lesion in the patient. A large number of T cells was present and TCD4+ cells (A) predominated over TCD8+ cells (B). Cells expressing tumor necrosis factor- α (TNF- α) (C) and transforming growth factor- β (TGF- β) (F) were present in high numbers, but only a few cells expressed interferon- γ (IFN- γ) (D) or interleukin-4 (IL-4) (E). Reactions were performed with streptavidin-biotin peroxidase (LSAB K690; Dako, Glostrup, Denmark) and primary antibodies mouse anti-CD4 (M834; Dako), mouse anti-CD8 (M 7103; Dako), goat anti-TNF- α (AF-210-NA; R&D Systems, Inc., Minneapolis, MN), mouse anti-IFN- γ (MAB 285; R&D Systems, Inc.), goat anti-IL4 (AF-204-NA; R&D Systems, Inc.), and rabbit anti-TGF- β (SC82; Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and streptavidin-biotin peroxidase (magnifications $\times 400$).

production and macrophage activation. At the same time, they increase IL-4 production and a shift toward Th-2 responses.²⁸ One study showed that corticosteroids caused a significant increase in the levels of parasitemia in patients with Chagas disease, depending on the dose and duration of treatment, although no overt cardiac decompensation was reported in these patients.²⁹

In our patient, ENN was accompanied by a systemic inflammatory reaction and multiple bacilli. The immunopathology of ENL was reviewed by Kahawita and Lockwood.⁶ Once considered fundamentally an immune complex-mediated phenomenon, more recent evidence also suggests that cell-mediated immune responses have a role. An immunohistochemical study of a biopsy lesion from our patient showed a rich T cell infiltrate with predominance of CD4+ cells over CD8+ cells (ratio of approximately 2.5:1) (Figures 3 and 4). However, with

FIGURE 4. Frequency of cells expressing the subpopulation markers (CD4 and CD8 cells) and cytokines (tumor necrosis factor- α , interferon- γ , interleukin-4 and transforming growth factor- β) in the patient detected by immunochemical analysis.

respect to the cytokine profile, this review reported that there is evidence for Th-1 and Th-2 involvement.⁶ Our patient illustrates this duality by showing high numbers of cells expressing tumor necrosis factor- α and moderate numbers of cells expressing interferon- γ , IL-4 and transforming growth factor- β (Figures 3 and 4); IL-10 and IL-6 were nearly undetectable.

This report highlights the difficulties in diagnosing and managing heart failure in a patient with relapsing ENN and chronic Chagas disease. The lack of diagnosis of this chronic endemic infectious disease may result in serious clinical complications. This case report also emphasizes the importance of searching for co-infections, such as Chagas disease and other parasitic diseases, in patients with leprosy because reactions develop in up to 50% of these patients while they receive MDT, which require prolonged therapy with immunosuppressive drugs.⁵ This finding is an issue not only for areas to which diseases are endemic, but also for developed countries, which are increasingly assisting patients with these diagnoses because of increased migration.

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