

## Short Communication

# Clinico-immunological spectrum of American tegumentary leishmaniasis and leprosy coinfection: A case series in Southeastern Brazil

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### Abstract

**Introduction:** American tegumentary leishmaniasis (ATL) and leprosy share common areas of prevalence, but reports of coinfection are scarce. **Methods:** We report a series of 9 ATL-leprosy cases and discuss the association. An integrative diagram to analyze the clinico-immunological features of coinfection with both diseases. **Results:** Nine patients with leishmaniasis (5 cutaneous, 3 mucocutaneous, 1 disseminated case) exhibited concurrent infection with distinct clinical forms of leprosy. Our diagram-based analysis evidenced a divergent clinico-immunological spectrum for each disease in 8 out of 9 cases. **Conclusions:** The spectrum of ATL-leprosy comorbidity suggests that the host has a specific immune response against each pathogen.

**Keywords:** Leishmaniasis. Leprosy. Coinfection. Cutaneous leishmaniasis. Mucocutaneous leishmaniasis.

American tegumentary leishmaniasis (ATL) and leprosy remain the major neglected diseases in some developing countries<sup>1,2</sup>. Leishmaniasis encompasses a spectrum of vector-borne parasitic infections caused by protozoa belonging to the genus *Leishmania*, which is represented mainly by the species *Leishmania (Leishmania) amazonensis* and *Leishmania (Viannia) braziliensis*, in Brazil<sup>1</sup>. ATL caused by *L. (V.) braziliensis* initiates as a single skin ulcer or as multiple skin ulcers that can be followed by mucosal involvement months or years later<sup>1</sup>. Leprosy is a chronic infectious disease caused by the non-cultivable bacillus *Mycobacterium leprae* that affects the skin and peripheral nerves<sup>2</sup>. Both diseases have become important public health concerns due to their wide geographic distribution, high incidence rates, and clinical manifestations with subsequent permanent serious injuries and mutilations<sup>1,2</sup>.

ATL and leprosy are endemic to Brazil, where most of the new cases in the Americas emerge<sup>1,2</sup>.

Although both diseases are prevalent in some countries, reports on comorbidity in the same patient are scarce. In 1978, 8 patients with coinfections of leprosy and cutaneous leishmaniasis (CL) were reported in Ethiopia<sup>3</sup>, followed by reports of ATL-leprosy concurrence in Venezuela<sup>4</sup>, India<sup>5,6</sup>, Northeastern Brazil<sup>7</sup>, Southeastern Brazil<sup>8-12</sup>, and Central America<sup>13</sup>.

ATL and leprosy share some intriguing features, as both are caused by obligate intracellular organisms and characterized by a spectrum of clinico-immunological manifestations that depend on T-cell-mediated immunity<sup>14,15</sup>. Intracellular pathogens such as *M. leprae* and *Leishmania spp.* can be effectively controlled by the Th1 CD4<sup>+</sup> subpopulation of the T-cell response. The immune hyperergic pole of both ATL and leprosy is characterized by a strong macrophage activation stimulated mainly by interferon (IFN)- $\gamma$  and interleukin (IL)-2. Clinically, the Th1 pole of leprosy is represented by the paucibacillary (PB) forms indeterminate (I), tuberculoid (TT), and borderline-tuberculoid (BT) of the Ridley–Jopling classification<sup>2</sup>, and that of ATL by the mucocutaneous leishmaniasis (ML) form<sup>1</sup>. These clinical forms typically show a strong reaction in the intradermal lepromin

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(or Mitsuda) test and the leishmanin (or Montenegro) test, respectively. Furthermore, the anergic pole is characterized by a depressed specific T-cell response with Th2 pole predominance. This pole is represented by the multibacillary (MB) clinical forms of leprosy, borderline–borderline (BB), borderline-lepromatous (BL), and lepromatous leprosy (LL), and by the diffuse anergic cutaneous form of leishmaniasis (CL) caused by *L. (L.) amazonensis* or the disseminated form (DL) caused by *L. (V.) braziliensis* infection<sup>14,15</sup>. Although ATL-leprosy coinfection in an immunocompetent patient is still a rare occurrence, it is a comorbidity of growing concern. The specific immune response to one disease seems to influence the clinical picture of the other, which explains the unpredictable course and difficult management of both infections occurring in the same patient<sup>10</sup>.

We aimed to report a case series of ATL-leprosy coinfections on the basis of an integrative diagram that emphasizes the clinico-laboratory features to establish a possible Th1/Th2 immunological spectrum relationship between these infectious diseases.

Diagnoses of ATL and leprosy were confirmed on the basis of the World Health Organization recommendations<sup>1,2</sup>. For ATL diagnosis, exclusive skin involvement was defined as the CL form, whereas lesions affecting the skin and mucosa or just the mucosa were classified as the ML form. Patients with 10 or more pleomorphic lesions in 2 or more body parts were classified as having DL. The Ridley–Joplin classification was used to determine the clinical form of leprosy<sup>2</sup>. Leishmanin<sup>1</sup> and lepromin<sup>2</sup> intradermal tests were performed to assess the cellular immune response. Enzyme-linked immunosorbent assay (ELISA) with an anti-phenolic glycolipid 1 (PGL1) antibody was conducted to measure the humoral response associated with leprosy<sup>2</sup>. Patients were negative for HIV and hepatitis B and C serology, except for case 9 who was positive for hepatitis C. ATL diagnosis was confirmed by polymerase chain reaction (PCR) using primers (forward: based on a minicircle kDNA from the *Leishmania* sp. 120-bp sequence 5'-(G/C)(G/C)(C/G)CC(A/C)CTAT(A/T)TTACACCCAACCCC-3', reverse: 5'-GGGGAGGGCGTTCTGCGAA-3') based on the sequence of a minicircle kDNA of *Leishmania* spp rendering a 120-bp PCR product. The ATL subgenus *Viannia* was identified by consecutive digestion of the PCR product with the restriction enzymes *Hae*III and *Bsr*I. Leprosy was diagnosed by PCR with primers targeting a 336-bp sequence of the *M. leprae* gene *MntH* (forward: 5'-CGGCTTCACGTCCAGTTTCTTC-3', reverse: 5'-TAAGTGCCCTCGATGTAAGCGG-3').

Based on the clinico-immunological spectra of ATL and leprosy described in the literature<sup>14,15</sup>, we generated an integrative figure to identify overlaps between the clinical forms of ATL and leprosy in terms of immunological spectrum and intradermal tests (cellular immune response), serology (humoral response), and histopathology (presence or absence of pathogen)<sup>14,15</sup>. This diagram served to clarify and compare the association between both diseases in this case report series (**Figure 1A**).

The 9 cases were also presented based on their clinical, laboratory, and immunological spectra to identify associations between both diseases (**Figure 1B**). **Tables 1 and 2** summarize

the demographical, clinical, and laboratory features of each patient.

In 3 cases (patients 4, 8, and 9) the subgenera *L. Viannia* and *M. leprae* were simultaneously identified by PCR in the same skin or mucosa sample. Three patients (cases 1, 2, and 6) were initially diagnosed with ATL, were treated and cured, and presented again later with clinical features of leprosy. In the remaining 3 patients, the order of disease manifestation was opposite: they first presented with leprosy and later exhibited clinical features of ATL during or after leprosy treatment (cases 3, 5, and 7).

ATL and leprosy share a clinico-immunological spectrum ranging from a strong T-cell response to a predominant B-cell response<sup>14,15</sup>, but we are the first to compare the spectra of both diseases in a case series.

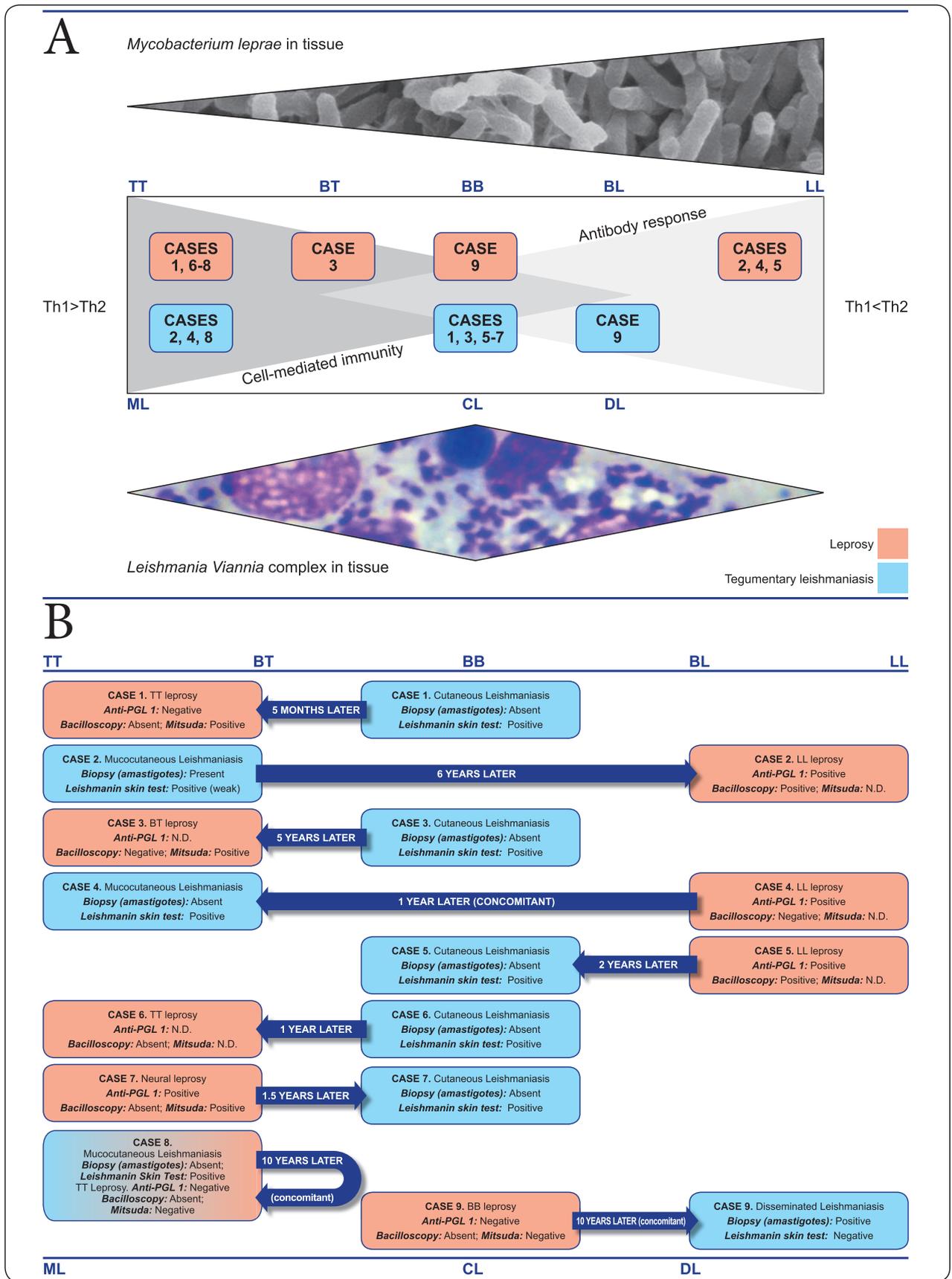
Concurrent ATL and leprosy have previously been reported<sup>3-5,12</sup>. Initial MB leprosy manifestation followed by clinical ML several years later has also been described<sup>10</sup>. Both ML and MB leprosy cause latent infections and sometimes decades elapse before these diseases become clinically recognizable<sup>14,15</sup>, which complicates determination of the time of infection and concomitant manifestation.

The delay in clinical manifestations may also reflect lack of adherence to treatment of one or both diseases<sup>7</sup>. Case 4 was treated with irregular multidrug therapy for leprosy for 1 year following clinical manifestation of ML, making it practically impossible to determine which disease was contracted first due to the long latency of both diseases. A case series in Ethiopia<sup>3</sup> identified patients that presented with leprosy for 2 to 7 years before clinical manifestation of CL. Nevertheless, an exact comparison with our study is difficult because *L. (L.) tropica* was the causative pathogen in these patients. Likewise, comorbidity of leishmaniasis with the BL clinical leprosy form<sup>5</sup> and TT leprosy<sup>6</sup> has been reported in India. Nevertheless, the anergic pole was attributed to the *Leishmania* spp. complex.

The subgenus *L. Viannia* was identified in a patient with LL in Venezuela that also showed CL association 5 years after leprosy was diagnosed<sup>4</sup>. In 2002, Goulart et al.<sup>8</sup> reported the first association between ATL caused by the subgenus *L. Viannia* and leprosy in Southeastern Brazil. Interestingly, this patient presented with the BL leprosy form with septal obstruction and was diagnosed with ML 3 years later<sup>8</sup>, a pattern resembling the time-lapse observed in our case 4. Since then, 8 cases have been reported in the state of Maranhão in Northeastern Brazil, 7 of which experienced BB-CL comorbidity and 1 CL associated with indeterminate leprosy<sup>7</sup>.

Genetic variations have been related to infectivity and pathogenicity of *Leishmania*. Certain *L. (V.) braziliensis* strains were proposed as causative pathogens for DL which is an emerging in Brazil but has never been reported as a coinfection with leprosy (patient 9). The concomitant chronic hepatitis C infection of this patient may have increased the susceptibility to ATL and leprosy coinfection.

ML is allocated to the maximum resistance pole of the Th1 immune profile. This exacerbated immune response accounts for local mucous destruction<sup>14</sup>. The immune response of ML patients did not resemble the immune spectrum of leprosy in this study<sup>10</sup>



**FIGURE 1.** (A) Clinical and immunological spectra of American tegumentary leishmaniasis and leprosy and placement of the reported 9 cases within the proposed spectra. (B) Clinical laboratory features of each patient according to the clinical spectrum for leprosy and American tegumentary leishmaniasis. **BB:** borderline-borderline, **BL:** borderline-lepromatous, **BT:** borderline-tuberculoid, **CL:** cutaneous leishmaniasis, **DL:** disseminated leishmaniasis, **LL:** lepromatous leprosy, **ML:** mucocutaneous leishmaniasis, **N.D.:** not determined, **PGL:** phenolic glycolipid 1, **TT:** tuberculoid leprosy.

**TABLE 1:** Clinical and immunological features of the initially diagnosed disease of 9 patients with American tegumentary leishmaniasis and leprosy in Southeastern Brazil.

Cases	Age (years)	Sex	Occupation	Initial clinical presentation	Disease duration (months)	Initial tests	Initial Treatment	Diagnosis
1	53	M	Farmer	Malar ulcer	5	LST + Amastigotes - PCR ( <i>L. Viannia</i> complex) +	MA	CL
2	68	M	Farmer	Nasal mucosal infiltration and ulceration	6	LST ± Amastigotes +	MA followed by Amphotericin B	ML
3	49	M	Truck driver	Anesthetic lesions on the trunk, abdomen, and legs	-	Mitsuda + AFB - Bacilloscopy -	MDT	BT
4	64	M	Farmer	LL (treated in primary health post). Squeals such as atrophy of interosseous hand muscles and bilateral ulnar thickening	-	Mitsuda N.D. Anti-PGL1 + Bacilloscopy -*	MDT	LL
5	54	M	Retired	Diffuse infiltrated erythematous lesions, bilateral ulnar thickening	-	Mitsuda N.D. Anti-PGL1 + AFB + Bacilloscopy +	MDT	LL
6	22	F	Student	Skin ulcers on the right forearm and left malar region	36	LST + Amastigotes -	MA	CL
7	66	M	Janitor	Sensitivity reduced on the dorsum of the left foot and paresthesia in the left leg	12	Mitsuda + Anti-PGL1 + Bacilloscopy	MDT	Neural TT
8	84	M	Farmer	Nasal septum ulcer	-	LST + Amastigotes - PCR ( <i>L. Viannia</i> complex) +	MA (irregular)	ML
9	58	M	Retired	Sensitivity reduced on the dorsum	60	LST - Anti-PGL1 - Bacilloscopy -	MDT (irregular)	BB

**AFB:** acid-fast bacilli; **BB:** borderline-borderline; **BL:** borderline lepromatous; **BT:** borderline tuberculoid; **CL:** cutaneous leishmaniasis; **DL:** disseminated leishmaniasis; **F:** female; **LL:** lepromatous leprosy; **LST:** leishmanin skin test; **M:** male; **MA:** meglumine antimoniate; **MDT:** multidrug therapy; **ML:** mucocutaneous leishmaniasis; **PCR:** polymerase chain reaction; **PGL1:** phenolic glycolipid 1; **TT:** tuberculoid leprosy; **+**: positive test result; **-:** negative test result; **±:** weak reaction in the test; **\***: post-treatment.

(**Figure 1**). For example, case 2 presented with the LL form in the anergic pole, and high levels of anti-PGL1 antibodies and presence of bacillus-forming globias in the skin confirmed the Th2 immune pattern and consequently deficient macrophage activity in this patient. Nevertheless, the patient exhibited the ML hyperergic pole representing ATL with granulomatous infiltrate and the amastigote form of *Leishmania* spp. was still present in the histopathological exam. Case 4 also presented with ML with no evidence of previous cutaneous ulcers but with concurrence of the LL clinical form.

The complex interaction between the parasite and the immune response of the host may complicate the interpretation of the ATL spectrum. ML induces a strong Th1 response resulting in a granulomatous immune response. Nonetheless, ML usually results from previous CL that disseminated to the mucosa via the blood or lymphatic system, a process that is probably attributed to failure in the local cellular immune response<sup>10</sup>. Thus, it appears that ML should not be placed within the spectral pole of a strong T-cell immune response.

The fact that the immune response of the host to each of the pathogens may alter the course of the other disease may lead to a clinical picture that differs from that expected for each

disease alone, and physicians should be aware that the diagnosis of coinfection could be challenging. Azeredo-Coutinho et al.<sup>10</sup> reported a case of LL with an IL-10-mediated regulatory response controlling the ML immunopathology, which may explain the opposing spectral Th1/Th2 poles for leprosy and ATL observed in cases 2 and 4. Moreover, the genetic profile of the host should be carefully analyzed to identify specific predispositions for ATL and leprosy that possibly explain the infrequent occurrence of both diseases in the same patient.

To our knowledge, this is the first study proposing a comparison between the clinical and laboratory features of ATL and leprosy based on the Th1/Th2 immunological spectrum. The diagram shown here could prove useful to researchers and physicians working in areas where leprosy and leishmaniasis are prevalent (**Figure 1A**).

Due to the retrospective character of this case series, the genetic background of the patients and certain other parameters such as the immunological profile (e.g., cytokines) and interurrences during disease progression were not analyzed. Nonetheless, we described important immunological tests and clinical features, allowing us to conduct a clinico-immunological comparison of both diseases in 9 patients.

**TABLE 2:** Clinical and immunological features of the secondary disease of 9 patients with American tegumentary leishmaniasis and leprosy in Southeastern Brazil

Cases	Time to secondary clinical manifestation (months)	Secondary clinical presentation	Secondary test	Diagnosis
1	5	Anesthetic lesions in the neck and abdomen	Mitsuda + Anti-PGL1 – AFB – PCR ( <i>M. leprae</i> ) + Bacilloscopy –	TT
2	72	Facial infiltration, cilia loss, generalized erythematous lesions, and compromised peripheral nerve	Mitsuda N.D. Anti-PGL1 + Bacilloscopy +	LL
3	60	Ulcer in the left knee	LST + Amastigotes – PCR ( <i>L. Viannia</i> complex) +	CL
4	12 (Still under MDT for leprosy)	Friable granulomatous vegetative nasal lesion	LST+ Amastigotes – PCR ( <i>L. Viannia</i> complex) + PCR ( <i>M. leprae</i> ) +	ML
5	24	Trunk ulcer	LST + Amastigotes – PCR ( <i>L. Viannia</i> complex) + PCR ( <i>M. leprae</i> ) +	CL
6	12	Red grouped papules on the left malar region near the leishmaniotic scar	Mitsuda N.D. Anti-PGL1 N.D. Bacilloscopy – PCR ( <i>M. leprae</i> ) +	TT
7	18	Ulcer on the right forearm	LST + Amastigotes – PCR ( <i>L. Viannia</i> complex) +	CL
8	120	Erythematous macule in the right thigh associated with anesthesia for thermic sensitivity and pain	Mitsuda – Anti-PGL1 – Bacilloscopy – PCR ( <i>M. leprae</i> ) +	TT
9	120	10 ulcers on the posterior region of the neck, in the left arm, and in the trunk	LST – Amastigotes + PCR ( <i>L. Viannia</i> complex) + PCR ( <i>M. leprae</i> ) +	DL

**AFB:** acid-fast bacilli; **BB:** borderline-borderline; **BL:** borderline lepromatous; **BT:** borderline tuberculoid; **CL:** cutaneous leishmaniasis; **DL:** disseminated leishmaniasis; **LL:** lepromatous leprosy; **LST:** leishmanin skin test; **MA:** meglumine antimoniate; **MDT:** multidrug therapy; **ML:** mucocutaneous leishmaniasis; **PCR:** polymerase chain reaction; **PGL1:** phenolic glycolipid 1; **TT:** tuberculoid leprosy; **+**: positive test result; **–:** negative test result; **±:** weak reaction in the test; **\***: post-treatment.

The cases described herein included patients that were particularly susceptible to a coinfection with ATL and leprosy because they live in an area where both diseases are endemic. Although epidemiological susceptibility is probably the most important risk factor for contracting both diseases, immunological and genetic conditions that favor a coinfection cannot be excluded.

The present study has shown no correlation between the Th1/Th2 immunological spectra of the clinical forms of ATL and leprosy in this case series, which suggests a specific host immune response against each pathogen. Increasing incidence rates of ATL and leprosy concurrence must be acknowledged to improve diagnostic and therapeutic strategies in regions where both diseases are prevalent.

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