Case Report

Vasculonecrotic Reaction in an HIV/Leprosy Coinfected Subject Caused by *Mycobacterium lepromatosis* Infection

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Case Report

Vasculonecrotic Reaction in an HIV/Leprosy Coinfected Subject Caused by *Mycobacterium lepromatosis* Infection

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Abstract: Background: Vasculonecrotic reactions in leprosy are often present in the context of a type 2 leprosy reaction. Differentiation between necrotizing erythema nodosum leprosum (nENL) and Lucio's phenomenon (LP) can be difficult, and cases of overlapping reactions have been reported. *Mycobacterum lepromatosis*, a relatively new species causing leprosy, has been sporadically reported to cause LP. Type 1 leprosy reaction occurs more commonly in HIV-coinfected individuals, and only sporadic cases of LP and ENL have been reported in the context of unmasked or paradoxical immune reconstitution inflammatory syndrome (IRIS). **Methods:** We present a case of a vasculonecrotic reaction in an antiretroviral-naive leprosy/HIV-coinfected individual caused by *M. lepromatosis*. **Results:** The patient had a 2-month course of papules and nodules that evolved into painful necrotic ulcers accompanied by systemic symptoms. The lesions were consistent with nENL; however, the histopathological findings were more consistent with LP. The patient rapidly progressed to sepsis and died. **Conclusions:** Vasculonecrotic reactions are considered a life-threatening medical emergency, and sepsis is a common complication. To our knowledge, this is the first reported case of a leprosy vasculonecrotic reaction in an HIV-infected individual not associated with IRIS caused by *M. lepromatosis*. Leprosy vasculonecrotic reactions may not be easily recognized in HIV-infected individuals, particularly those with severe immunosuppression, where opportunistic infections, especially fungal infections, malignant syphilis, and other mycobacteriosis, may present similar findings. Delayed diagnosis can lead to severe complications and risk of death.

Keywords: Vasculonecrotic reaction; Leprosy; HIV infection; *Mycobacterium lepromatosis*; necrotizing erythema nodosum leprosum; Lucio's phenomenon; Leprosy reactions

1. Introduction

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* or *Mycobacterium lepromatosis*. Both species are closely related with 13% genetic difference in nucleotide sequence [1] and have a common ancestor with a divergence of 13.9 million years ago [2].

Leprosy reactions (LR) are immunological episodes that can occur before, during or after leprosy treatment and these can be stimulated by *M. leprae* antigens such as phenolic-glycolipid-I (PGL-I) or by co-infections [3].

Leprosy reactions are classified as type 1 leprosy reaction (T1R), a cell-mediated reversal reaction characterized by the development of new lesions, exacerbation of those already present, thickening and tenderness of peripheral nerves occurring in people with tuberculoid leprosy (TL), borderline

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tuberculoid (BT), borderline (BB). In the other hand, type 2 leprosy reaction (T2R) or erythema nodosum leprosum (ENL) is associated with the formation of immune complexes in the blood that are deposited inside tissues, especially skin, kidneys and joints [3]. T2R occurs usually as an immunological complication of the clinical forms of borderline lepromatous (BL) and lepromatous leprosy (LL) [3]. Borderline forms are immunologically unstable and more predisposed to developing LR [4].

Vasculonecrotic reactions in leprosy occur as part of a type 2 leprosy reaction (T2R) including a severe form of necrotizing erythema nodosum leprosum (nENL) that occurs in BL or LL cases [5,6] and Lucio's phenomenon (LP) a leprosy reaction which occurs in an untreated anergic form of the disease, named diffuse lepromatous leprosy (DLL), although it can also be presented in LL and BL forms[5]. These two reactions can be difficult to differentiate [7,8].

We present a case of a fatal vasculonecrotic reaction in a HIV/leprosy coinfected patient caused by *M. lepromatosis* Infection.

2. Case Presentation

A 33-year-old male with a recent diagnosis of HIV infection, originally from Jalisco and resident from Aguascalientes, Mexico. He started 2 months before his hospital admission with violaceous papules and nodules that evolved into painful necrotic ulcers, which began on the trunk and later appeared on the limbs and face, associated with malaise, weight loss, fever and nocturnal diaphoresis. Fifteen days prior to his hospitalization, he had loss of vision in his right eye. The physical examination revealed deep, punched-out ulcers of variable size, ranging from 5 to 20 mm, round and ovoid in shape with regular edges **(Figure 1).** The ophthalmological evaluation showed blindness in the right eye, retinal detachment with hemorrhagic and fibrotic lesions compatible with cytomegalovirus chorioretinitis, accordingly ganciclovir was started. The HIV-1 RNA was 301,000 copies/μL and CD4+ T cells count 4 cells/mm^3. Significant laboratory findings included Hb 9.4g/dL, leukocytes 3.76 10^3/μL, GGT 176 IU/L, albumin 2.4g/dL, ALT 199 U/L, AST 331 IU/L, alkaline phosphatase 215 IU/L, lactate dehydrogenase 486 U/L, VDRL positive, title 1:1. Abdominal US showed hepatomegaly with steatosis.

A skin biopsy of a lesion revealed ulceration and necrosis of the epidermis with acute inflammatory infiltrate at the expense of polymorphonuclear cells, the dermis exhibited extensive chronic histiocytic inflammatory infiltrate of neurotropic behavior, besides, a panniculitis pattern of inflammation of the subcutaneous cellular tissue, leukocytoclastic vasculitis and thrombosis was observed. A CD68 immunohistochemistry revealed macrophages located perineurally. A Fite-Faraco stain resulted positive to abundant acid-fast bacillus (AFB) Based on the histopathological findings a lepromatous leprosy with Lucio's phenomenon was diagnosed **(Figure 2)**.

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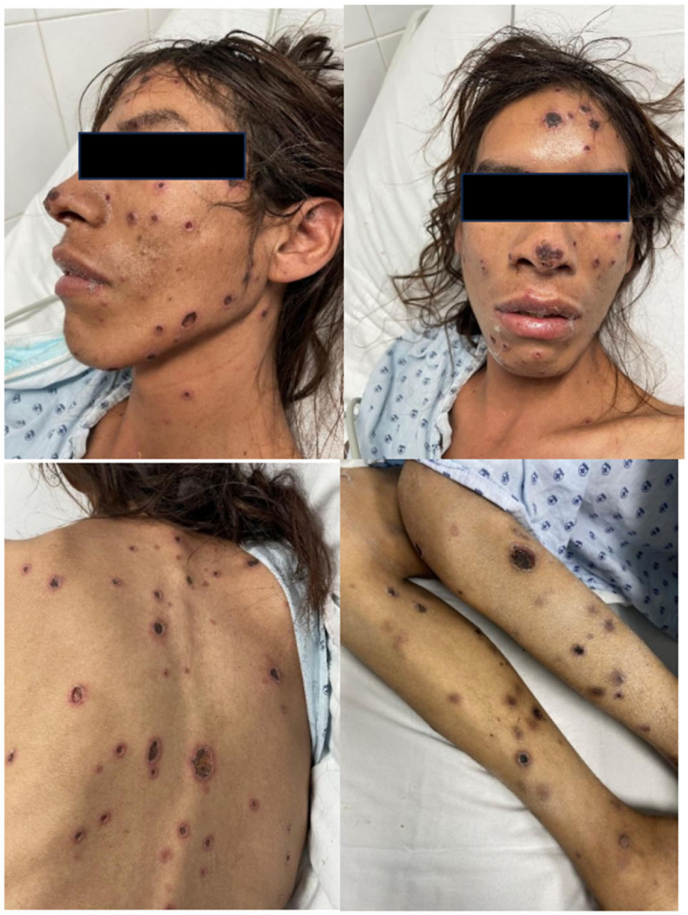

Figure 1. (a, b) Multiple deep, punched-out ulcers, well-demarcated, covered by necrotic eschars. Some papules and nodules are evolving into necrotic ulcers on the face. (c) Ulcers on the back have an erythematous halo and (d) ulcers on extremities are in a later stage.

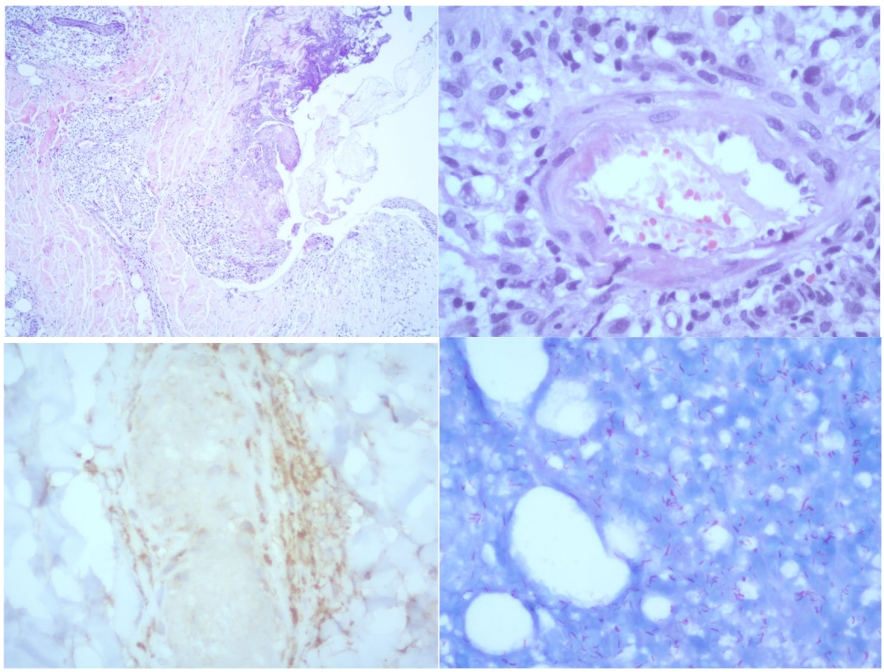

Figure 2. Histopathology of a skin biopsy showing: (a) Epidermis with reactive changes, ulceration and necrosis of the epithelium, with acute inflammatory infiltrate at the expense of polymorphonuclear neutrophils (H&E,

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X5). (b) leukocytoclastic vasculitis (H&E, X40). (c) CD68 immunohistochemistry, positive immunostaining of perineurally located macrophages (X40). (d) Multiple acid-fast bacillary structures inside and outside the macrophages (Fite-Faraco stain, X40).

A PCR from the skin tissue was obtained to identify the microorganism. Using a 1% agarose gel, we carry out a PCR with the LPMF-244 Primers, a *hemN* gene region specific to *Mycobacterium lepromatosis* (absent in other known mycobacteria) **(Figure 3)**

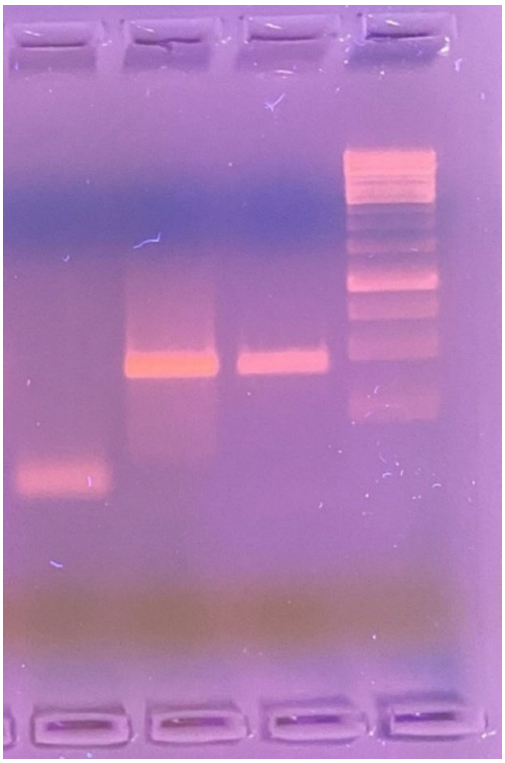

Figure 3. 1% agarose gel (left to right): Negative control: Sterile saline solution. **Positive control:** Sample from a patient with confirmed *M. lepromatosis* infection. **Test sample:** Amplified with LPMF-244 primers targeting a *hemN* gene region specific to *Mycobacterium lepromatosis* (absent in other known mycobacteria) 100 bp.

During hospitalization, the patient developed septic shock treated with antibiotics (vancomycin and meropenem) and vasopressors, but he did not respond to the treatment and finally died from septic shock.

3. Discussion

In this report, we describe the case of a vasculonecrotic reaction with systemic symptoms caused by M. lepromatosis in a HIV-infected subject who was unaware of having leprosy, with severe immunosuppression, naive to antiretroviral treatment, who rapidly progressed to sepsis with fatal outcome.

Vasculonecrotic lesions in leprosy occur on T2R and most frequently are presented as a complication of the anergic form of diffuse lepromatous leprosy[8,9]. Differentiation between nENL and LP can sometimes be difficult and there are reported cases of overlapping of both reactions [5,7,8,10]. Clinical and histopathological findings are essential for diagnosis [11].

Clinically, nENL is characterized by nodular lesions that develop necrosis and painful ulcers, it is accompanied by systemic symptoms including fever, myalgia, arthralgia, malaise, lymphadenopathy, iritis, episcleritis, hepatitis, neuritis, and orchitis, which usually appears after treatment has started [7]. In contrast, LP presents multiple and extensive purpuric areas with net-like

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pattern and superficial ulceration over areas of infiltrated skin[5]; polygonal with angled margins and jagged-edges ulcers eventually evolve to necrosis, which commonly affect extremities, it is accompanied by a burning sensation, leaving stellar atrophic scars; systemic symptoms and visceral involvement are usually absent; the lesions appear in untreated or inadequately treated non-nodular lepromatous leprosy and other forms of LL [7] and frequently presents as the debut of the disease without a previous leprosy diagnosis [11]. Our patient did not have a previous diagnosis of leprosy. A systematic review found that 42/49 (85.7%) of patients diagnosed with LP had no prior diagnosis of leprosy [12].

Histological nENL shows histiocytes in the dermis with infiltration of neutrophils in the deeper layer of the dermis, vasculitis and panniculitis with few bacilli present [12]. On the other hand, LP is characterized by many AFB aggregates in the vascular endothelium, leukocytoclastic vasculitis, endothelial cell proliferation[8], ischemic epidermal necrosis [12], necrotizing vasculitis on superficial and medium-sized vessels [13], and presence of fibrin thrombi [7].

The pathogenesis of LP is attributed to massive bacillary invasion into the vascular endothelium that leads to narrowing and subsequent occlusion of the lumen of the small vessels that progresses to thrombosis and skin necrosis, with a further secondary inflammatory response and deposition of immune complex [10]; immunofluorescence tests in LP often exhibit immune complexes of IgM, IgG, C3, and C1q in the walls of dermal blood vessels [14]. Differential diagnosis of LP includes cryoglobulinemia, leukocytoclastic vasculitis, pyoderma gangrenosum, antiphospholipid syndrome, and disseminated intravascular coagulation [15,16]. In contrast, in ENL the triggering event is an immunological process with the deposition of immune complexes [10].

Because of the high bacillary load in LP, treatment with multidrug therapy (MDT) is a priority accompanied by steroids, antibiotic, anticoagulants, surgical debridement and skin grafting for the wounds [17,18]. In contrast, the treatment of nENL is based on steroids and thalidomide [5].

M. lepromatosis was recognized in 2008 as a new species causing a fatal DLL in 2 Mexican patients [19]. Although *M. lepromatosis* is endemic in Mexico, it has also been identified less frequently in other regions in the Americas and sporadic cases in Asia [20–22]. The clinical presentation of *M. lepromatosis* infection is most frequently as DLL, a form of endemic leprosy in Mexico characterized by diffuse non-nodular cutaneous infiltration[22] described by Lucio and Alvarado in 1852 [23] and later recognized by Latapí and Chevez-Zamora in 1948 [24].

Han et al. found that of 87 species-confirmed cases of leprosy in Mexico, 63.2% were caused by *M. lepromatosis*, 20.7% by *M. leprae* and both species were identified in 16.1% of cases. In the *M. lepromatosis* group, 34/55 (61.8%) were diagnosed with LL, and the total of 13 cases of DLL (23.6% of 55 cases) were caused by *M. lepromatosis* [25]. These results differ from the findings of a study, which found that of 7 specimens positive for *M. lepromatosis* from Brazilian patients, all presented as tuberculoid leprosy (TL) suggesting that ethnicity could play an important role in clinical forms [26].

Both *M. leprae* and *M. lepromatosis* have been found by PCR of tissue in LP, which shows that both species can trigger this immunological reaction suggesting a host component, rather than the species of *Mycobacterium* would be responsible for this reaction [27]. Reported cases of LP associated to *M. lepromatosis* have been mostly from subjects originating from Mexico or the Caribbean [12,28–30].

HIV infection has altered the epidemiology of several mycobacterial infections particularly *M. tuberculosis* and *Mycobacterium avium intracellulare* complex infection, which have increased their prevalence and severity in these population [31], however the number of leprosy cases has not increased due to HIV infection and HIV seroprevalence among cases newly diagnosed with leprosy have not shown significant difference between case and control groups [32].

Since HIV primarily affects the host cell-mediated immune response, it was expected that there would be an increase in lepromatous leprosy in co-infected individuals; however, the clinical spectrum of leprosy has not been modified in HIV-infected patients[33].

The histopathological findings have not been modified by HIV infection either. A study compared the histological findings in patients co-infected with leprosy and HIV infection vs patients

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infected with leprosy alone and did not find histopathological differences between both groups. Typical histological lesions were found in co-infected patients with a granulomatous-type immune response [34]. Granuloma formation in leprosy has not been affected in co-infected subjects with HIV even with low CD4+ T-cell counts [36].

Nevertheless, an increased incidence of leprosy was observed within the first 3 months following initiation of antiretroviral (ARV) therapy because of immune reconstitution, although no significant difference was found in patients treated for more than 3 months [36]. Some cases of paradoxical immune reconstitution inflammatory syndrome (IRIS) after starting ARV therapy have been reported [37,38] principally manifested with leprosy T1R after improving cell-mediated immunity by increasing the CD4+ T lymphocyte count usually within the first six months of ARV therapy, mostly in borderline forms predominantly BT form [39].

Although an increase in leprosy reactions has been reported in people co-infected with HIV/leprosy[40,41], a cohort study of 40 patients co-infected vs 107 patients non-HIV-infected followed for 2 years found no increase in frequency of leprosy reactions, 86.7% of the reactions in the co-infected group were T1R, 53.3% as a manifestation of IRIS and 93.3% of the patients were in AIDS stage, showing that several factors may influence the immune behavior of both diseases. The co-infected group did not present clinical or histological differences in the leprosy reactions presented vs the leprosy alone group [42].

The largest cohort of HIV/leprosy coinfected patients reported in Brazil found that of 92 coinfected subjects, 33 (36%) patients had a leprosy reaction at the time of diagnosis, of which 32 (97%) had T1R and the use of ARV therapy was the only factor associated with T1R [43]. Although T1R is clearly more common in co-infected patients, sporadic cases of LP and ENL have been reported in the context of unmasking or paradoxical IRIS [44–46].

LP is considered a life-threatening medical emergency [47] and sepsis is a frequent complication in subjects with LP due to bacterial superinfection of the lesions with fatal results [48]. Systemic antibiotics for sepsis were used in 15/49 (30.6%) of subjects with LP presenting a high mortality [12]. In the present case, the patient died from sepsis.

The clinical characteristics of the lesions presented in our case showed nodular lesions that evolved into deep painful necrotic ulcers with systemic symptoms (fever, malaise) consistent with nENL, while the histological characteristics corresponded to LP with skin necrosis, vasculitis and thrombosis with a high AFB load in an untreated patient with DLL. We consider that the severe lack of cell-mediated immune response in this HIV-infected patient with very low CD4+ T cells count led to a high bacillary load as revealed in the histopathological findings that triggered the known pathophysiological mechanisms of this reaction.

4. Conclusions

Vasculonecrotic reactions are considered a life-threatening medical condition. To our knowledge, this is the first case reported of leprosy vasculonecrotic reaction in HIV-infected subjects not associated with IRIS caused by *M. lepromatosis*. Leprosy vasculonecrotic reactions may not be easily recognized in HIV-infected individuals, where also atypical severe presentations of various infections may occur, including cutaneous cryptococcosis, disseminated sporotrichosis, malignant syphilis, cutaneous mycobacterial infections among others, hence the diagnosis is challenging. Delay in recognition of the disease can lead to untimely start of appropriate treatment with poor outcomes including devastating cutaneous damage, sepsis and high risk of death.

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Informed Consent Statement: Informed consent for publication was obtained from the patient for the case report and imaging.

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