Our Dermatology Online

Case Report

Morphea overlapping borderline leprosy: An unusual association

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ABSTRACT

Leprosy, or Hansen's disease, is a chronic infectious disease with a low transmission rate, affecting the skin, peripheral nerves, eyes, and mucous membranes of the upper respiratory tract, yet it may also be systemic. Cases of borderline leprosy are the acute or subacute stages of the disease. They are immunologically unstable and reflect the gradual variation in resistance against the etiological agent. Localized scleroderma or morphea is a fibrosing disease of the skin and underlying tissues that results from the disrupted function of growth factors (platelet-derived growth factor, i.e., PDGF) and receptor expression (as in the case of transforming growth factor β, i.e., TGF-β). Herein, we report a female patient with borderline tuberculoid leprosy (BT) who, during multidrug treatment (MDT), developed an indurated lesion of morphea exactly on the surface of an infiltrated patch.

Key words: leprosy; morphea; overlapping; borderline leprosy

INTRODUCTION

Leprosy, or Hansen's disease, is a chronic infectious disease with a low transmission rate, affecting primarily the skin, peripheral nerves, eyes, and mucous membranes of the upper respiratory tract, yet it may also be systemic. It is caused by *Mycobacterium leprae* and, in some cases, by *M. lepromatosis* [1]. Worldwide, it is an outstanding cause of morbidity due to the physical handicap and social stigma [1,2].

Cases of borderline leprosy are the acute or subacute stages of the disease. They are immunologically unstable and reflect the gradual variation in resistance against the etiological agent. Most progress to lepromatous leprosy. These patients develop infiltrated nodular or annular/circular plaques, which resolve with central atrophy. Some patients develop symmetrical neuropathy and areas of anesthesia [1,3].

Localized scleroderma or morphea is a fibrosing disease of the skin and underlying tissues that results from the disrupted function of growth factors (platelet-derived growth factor, i.e., PDGF) and expression of receptors (as in the case of the transforming growth factor β, i.e., TGF-β). There is an imbalance between collagen production and destruction found more frequently in females [1,4].

Herein, we report a female patient with borderline tuberculoid leprosy (BT) who developed an indurated lesion clinically and histologically compatible with morphea exactly on the surface of an infiltrated plaque during multidrug treatment (MDT) for multibacillary leprosy.

CASE REPORT

This was a 52-year-old female, a housewife from Merida, in the Yucatan peninsula of Mexico. Her

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medical history was non-contributory. She complained of a two-month history of a "growing hematoma" and lesions on the abdomen. An examination found three erythematous, well-demarcated, infiltrated plaques with a nodular appearance on the abdominal wall. The largest plaque was approx. 15 × 8 cm while the smallest, with an annular morphology, was 7 × 5 cm. There were no sensory abnormalities on the initial neurological examination (Fig. 1).

A skin biopsy of the initial lesion revealed an inflammatory infiltrate of epithelioid histiocytes surrounded by lymphocytes, forming granulomas around neural and adnexal structures. Occasional histiocytes with a foamy appearance were observed (Figs. 2a and 2b). The presence of acid-fast bacilli (AFB) was confirmed, with a bacteriological index of 1+ and a morphological index of 33%. Additionally, PCR identified *M. leprae*. The patient was classified as having borderline tuberculoid leprosy (BT). MDT was commenced with a good response and a significant improvement in the lesions.

After six months of follow-up, the patient complained of tenderness in the larger plaque. An examination revealed increased peripheral erythema associated with hardening and central hyperpigmentation (Figs. 3a and 3b). A second biopsy was performed, showing atrophy of the epidermis with diffuse hyperpigmentation of the basal layer. There was a lymphoplasmacytic interstitial infiltrate between the collagen bundles as well as around the eccrine glands and other adnexal structures. Loss of appendageal structures was also observed. Increased dense hyalinized collagen bundles with a sclerodermiform appearance extended to subcutaneous cellular tissue and were confirmed by Masson's trichrome stain (Figs. 4a and 4b). The diagnosis of morphea was established.

The patient was treated with 0.05% desonide cream twice a day applied to the indurated lesion for two months with an improvement. Over time, both the lesions of leprosy and those of morphea resolved with residual dyschromia (Fig. 5).

DISCUSSION

Patients with borderline leprosy have dynamic immunity with fluctuations in the course of the disease. These oscillations are the result of interactions

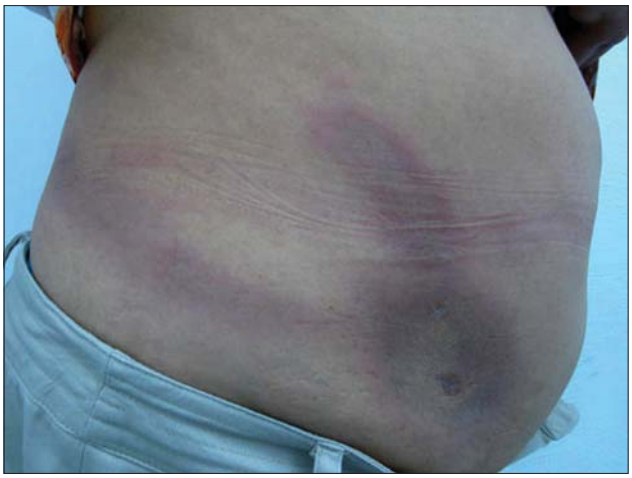

Figure 1: Erythematous, well-demarcated, infiltrated plaques on the abdominal wall.

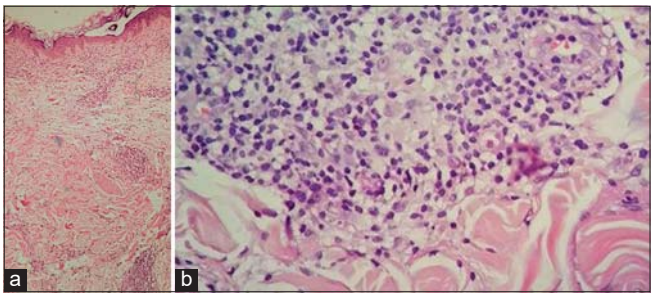

Figure 2: (a and b) Inflammatory infiltrate of epithelioid histiocytes surrounded by lymphocytes arranging granulomas around neural and adnexal structures (H&E; 10× and 40×).

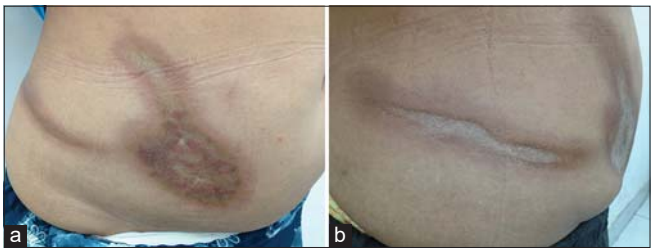

Figure 3: (a and b) Morpheaform aspect of the larger plaque during MDT.

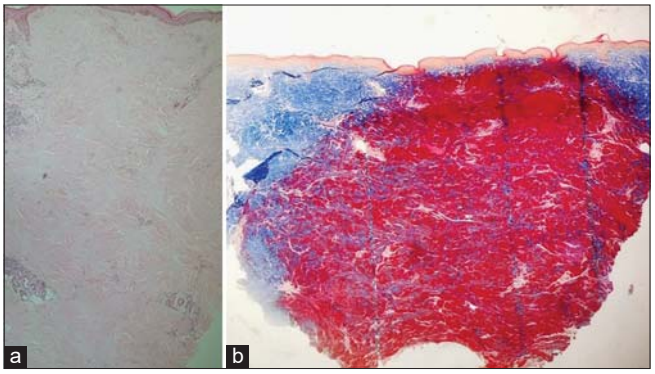

Figure 4: (a and b) Inflammatory, lymphoplasmacytic, interstitial infiltrate around the eccrine glands with hyalinized collagen bundles (H&E; 10×) (Masson's trichrome stain; 10×).

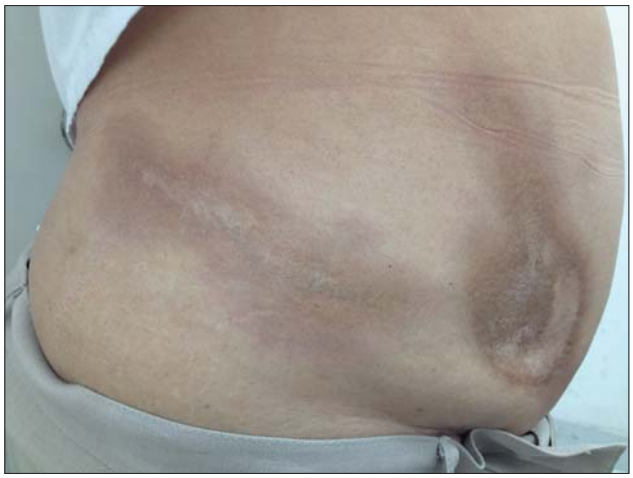

Figure 5: The remaining dyschromic plaque after MDT.

between multiple inner factors of the patient and the mycobacterium. Th1-type cytokines play a major role in the tuberculoid pole (IFNɣ, IL-2, IL-22, IL-15, and TNFα), as opposed to Th2-type, which are predominant in the lepromatous pole (IL-4, IL-10) with the formation of immune complexes [1,5,6].

It is well known that, after beginning adequate treatment, the immune response fluctuates. There is the reactivation of the cellular response with the production of inflammatory mediators associated with tissue damage [6].

Another group of cells that play an important role in the immune response against mycobacteria are Th17 cells, which perform a regulatory function. Depending on the closest pole they reside in, they trigger the synthesis of IL-17A, IL-17F, IL-21, and IL-22, which results in the recruitment of neutrophils and the activation of macrophages or the production of transforming growth factor β (TGF- β). Likewise, in patients with tuberculoid leprosy and in those with a type-1 reaction, a marked increase in ICAM-1 expression in keratinocytes and lymphocytes is classically seen [1,7].

Finally, lymphocytes may differentiate into Th9 and Th22 cell lines in the presence of IL-4 and TGF-β. These Th9 lymphocytes produce high amounts of IL-9, IL-10, and IL-21, which promote cytotoxicity against *M. leprae*; meanwhile, Th22 lymphocytes are characterized by the production of IL-22 and fibroblast growth factors, which are predominant as the patient approaches the lepromatous pole [7].

The pathogenesis of morphea is unknown. There is a functional disfunction of fibroblasts leading to increased synthesis of collagen and other extracellular matrix proteins [6]. Vascular damage, autoimmune factors, and skin fibrosis have been postulated as a result of triggering factors, such as physical damage, radiation therapy, trauma, and bacterial or viral infections, in which epitope extension or lymphocyte microchimerism takes place. Occasionally, a relationship with *Borrelia burgdorferi* infection was demonstrated by the presence of the microorganism in tissue samples or in antibodies against it [1,6].

The pathogenesis of fibrosis involves the presence of profibrotic factors that act on fibroblasts. These mediators, such as TGF-β, are secreted by lymphocytes, macrophages, and mast cells. Overexpression of receptors for TGF-β promotes increased levels of connective tissue growth factor (CTFG). Together, they increase levels of collagen and decrease the production of collagenases [1,6,8-10].

Overall, the immune response led by mononuclear cells results in the disruption of endothelial cells following microvasculature damage. There follows the production of chemotactic cytokines such as selectins, vascular adhesion cell molecules (VCAMs), intercellular adhesion molecules (ICAMs), interleukin (IL) -1, IL-2, IL-4, IL-6, and IFNɣ, and an active TH1 response. The consequence is the increase in the production of abnormal collagen with the deposition and storage of extracellular matrix components [1,10], different from lipomembranous changes seen in vascular or connective tissue diseases (systemic sclerosis), due to the interruption of blood supply with thickening and hyalinization of vessel walls [11].

In addition to platelets themselves, the hypersecretion of platelet-derived growth factor (PDGF) has been observed in different cell lines, such as fibroblasts, macrophages, epithelial cells, and nerve cells. Platelet-derived growth factor (PDGF) has a paracrine and autocrine chemoattractant and mitogenic effect in fibroblasts, resulting in the increase of collagen and the production of extracellular matrix components. Cells that express receptors for PDGF include fibroblasts, smooth muscle cells, capillary, and neuronal endothelial cells [12].

The histology of morphea is variable and depends on the stage of the disease. Overall, the epidermis is normal or atrophic. Incipient stages show thickening

of collagen and edema in the dermis associated with perivascular lymphoplasmacytic infiltrates, loosening of the adnexal structures, and vessels with wall thickening and luminal narrowing.

In the late stages, the inflammatory infiltrate tends to disappear, and the dermis shows thickening with dense collagen and reduced elastic tissue. There is a general loss of the adnexal structures and the presence of only some sweat glands in the deep sclerotic areas [1,13]. In some cases, there is a perineural distribution of these infiltrates without sensory abnormalities. The latter explains the disposition of lesions in a dermatomal pattern [14].

Comments

The immune response in dimorphic leprosy comprises a dynamic and oscillating spectrum with fluctuations both during the evolution of the disease and during treatment. Thus, cellular involvement and pro-inflammatory cytokines vary greatly depending on the predominant pole of the disease.

Acute reactions may appear in approx. 20% of cases, especially during pharmacological treatment with a greater release of mediators associated with tissue damage. These mediators include IFNɣ, IL-1 (typical of the tuberculoid pole) and IL-22 (which actives macrophages secreting TGF-β), ICAM-1, fibroblast growth factors (shared with scleroderma and which may be triggered in response to infectious processes). IL-1, IL-2, and IL-4 activate PDGF and CTGF, resulting in the chemoattractant effect on fibroblasts, with the excessive formation of collagen and a decrease in the production of collagenases.

It is likely that the coexistence of these two entities was provoked by either an infectious stimulus in a patient with a genetic predisposition or as a result of the immune adjustment activated by MDT. A significant inflammatory response may result from both, driven mainly by macrophages and the production of a dynamic cytokine profile. Furthermore, a potential cross-reaction with the stimulation of fibroblasts and profibrotic factors (microchimerism) cannot be excluded. The sclerotic changes may also be due to a physical injury with microvascular lesions, intercurrent infections, or stress (not reported in our patient) [15, 16].

In fact, some authors have previously reported several cases of leprosy mimicking connective tissue diseases with features of systemic lupus erythematosus, with the resolution of both disorders after MDT [17, 18]. In our patient, all lesions resolved with topical steroid therapy after concluding MDT. Some authors report the use of steroids with or without methotrexate, vitamin D analogs, colchicine, retinoids, antimalarials, pentoxifylline, broad-band UVA, phototherapy, Salazopyrin, or immunomodulators, systemic retinoids, and immunosuppressive drugs in resistant cases [19, 20]. In conclusion, we postulate that the fibrosing process resolved after the disappearance of the antigenic stimuli constituted by the bacilli and the cessation of the treatment-derived inflammation.

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