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Case Report

Leprosy and Lupus: Concurrence or Epiphenomenon

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Leprosy and systemic lupus erythematosus (SLE) share many clinical and laboratory characteristics. Azulay coined the term "autoaggressive hanseniasis" (AH) to describe multibacillary leprosy cases exhibiting clinical and immunologic features reminiscent of autoaggressive connective tissue diseases. This article presents the case of a 20-year-old Nepalese woman diagnosed with borderline lepromatous leprosy, demonstrating both clinical and laboratory evidence of autoimmune connective tissue disease. Treatment comprising a multidrug leprosy regimen alongside thalidomide and corticosteroids led to a remarkable clinical improvement. The discussion emphasizes the importance of recognizing rheumatic symptoms in leprosy cases, thereby averting misdiagnosis with autoimmune disorders, and underscores the therapeutic efficacy of thalidomide. Furthermore, we endeavor to address the diagnostic challenge surrounding autoaggressive hanseniasis in contemporary practice, pondering whether it represents a distinct clinical entity or manifests as multibacillary leprosy with clinical-serological evidence of autoimmune connective tissue diseases.

Keywords: Leprosy, Lupus, Autoaggressive Hanseniasis, Autoimmune Connective Tissue Disease

Introduction

Leprosy and systemic lupus erythematosus (SLE) share many clinical and laboratory characteristics. The term **"**autoaggressive hanseniasis"(AH) was first coined by Azulay in 1987 to describe such presentations in lepromatous leprosy (LL), infrequently, in borderline lepromatous leprosy (BLL), where clinical and immunologic features akin to autoaggressive connective tissue diseases are observed. The probable etiology involves the activation of B lymphocytes by antigenic complexes of *Mycobacterium leprae*, coupled with autologous tissue interaction and dysfunction of T-suppressor lymphocytes (Azulay 1987). Here, we represent a case of borderline lepromatous leprosy, showcasing both clinical and laboratory evidence of autoimmune connective tissue disease.

Case Report

A 20-year-old housewife presented with a two-month history of skin lesions over her body, accompanied by fever. Initially asymptomatic, she later developed multiple, raised, painless, skin-coloured lesions on her lower limbs, which gradually spread to the upper limbs, trunk, and face. Although the lesions exhibited a tendency to self-heal, they recurred intermittently. The skin manifestations were concomitant with low-to-

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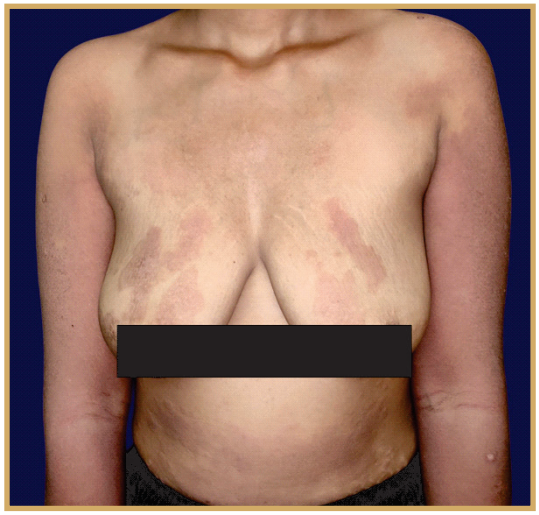

Fig. 1a

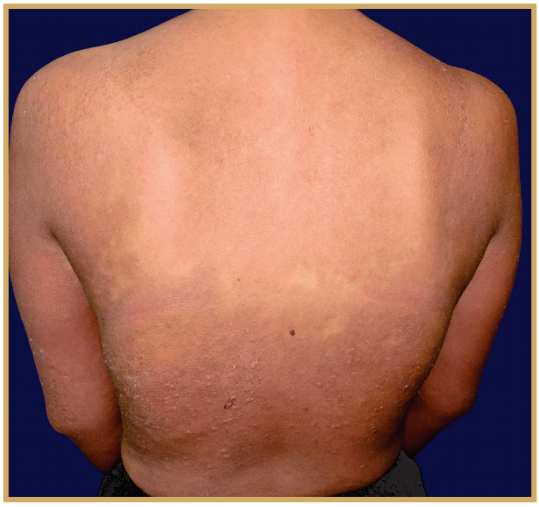

Fig. 1b

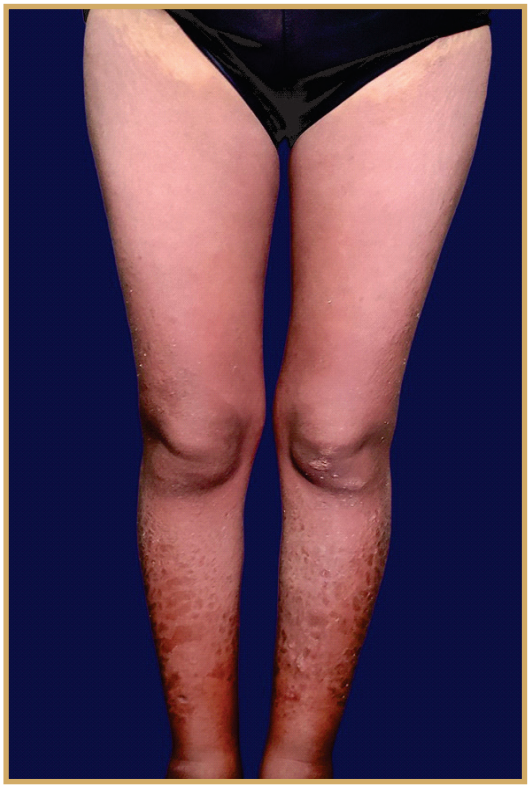

Fig. 1c

Figs. 1a, 1b, 1c (pre-treatment): Multiple, well defined, non-tender, erythematous, blanchable plaques present over both upper limbs, lower limbs, breasts, lower abdomen (1a), lower back (1b) and face along with multiple, small, non-tender, skin coloured to erythematous blanchable papules scattered over it. Ichthyotic changes are noticeable over lower legs (1c).

moderate grade intermittent fever, accompanied by chills, malaise, and arthralgia. Additionally, she experienced edema of the hands and feet for two weeks, with exacerbations in the morning. There was no history of accidental slippage of footwear, bleeding from the nose, or redness of the eyes. The patient had sought consultations from multiple physicians in Nepal regarding her current complaints.

Upon examination, she was febrile (38°C) and moderately anaemic with bilateral pitting edema of the hands and feet. A cutaneous examination revealed diffuse blanchable erythema over both upper and lower limbs as well as the back (Figs. 1a,1b,1c). Multiple small, non-tender, skin coloured to erythematous, blanchable papules were observed on the lower back (Fig. 1b). A few well-defined, non-tender, erythematous, blanchable plaques were noted on the breasts and lower abdomen (Fig. 1a). Bilateral ear lobe infiltration was evident, along with noticeable ichthyotic changes on the lower legs (Fig. 1c). Bilateral ulnar nerves were thickened, but non-tender. Loss of hot and cold differentiation, touch, and pain sensation was noted over the ulnar side of both hands. The power of the small muscles of the hands and feet was graded as 5. The examination of the cranial nerves, eyes, and mucosa were unremarkable. Lymph nodes were not palpable. There was no organomegaly, and examination of the cardiovascular, respiratory, and alimentary systems was non-contributory. Borderline lepromatous leprosy, systemic lupus erythematosus, Sweet syndrome, and papular mucinosis were considered differential diagnoses.

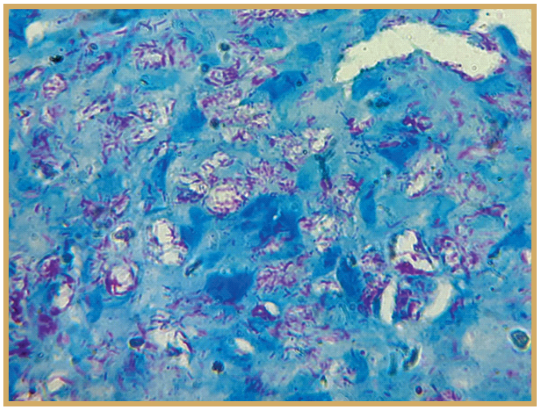

Fig. 2 : Slit skin smear showing rod-shaped pinkish viable acid-fast bacilli (Ziehl-Neelsen stain, oil immersion, 1000x).

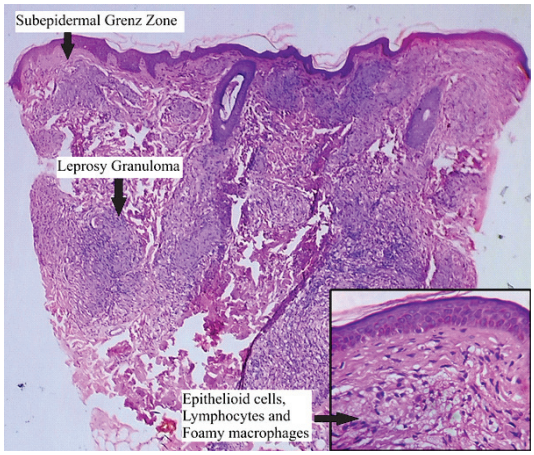

Fig. 3 : Histopathology revealed a thinned-out epidermis, subepidermal grenz zone, and leprosy granuloma in underlying dermis in curvilinear fashion. Granuloma is composed of aggregates of epithelioid cells, lymphocytes, histiocytes, Langhan's giant cells and foamy macrophages (H & E, 40x) (Better appreciated in inset image: H & E, 400x).

Slit-skin smears (SSS) from ear lobes revealed solid and fragmented acid-fast bacilli in the Ziehl-Neelsen stain, with a bacterial index (BI) of 6+ and morphological index (MI) of 70% (Fig. 2). Histopathological examination of skin samples from papules of the face and left shoulder both showed a thinned-out epidermis, subepidermal grenz zone, aggregates of epithelioid cells, lymphocytes, histiocytes, Langhan's giant cells,

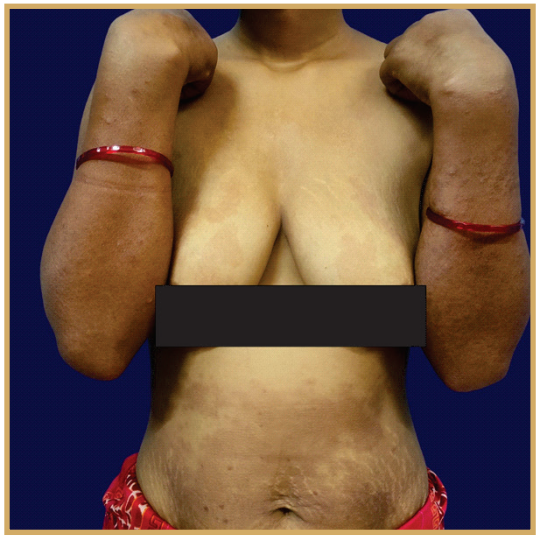

Fig. 4a

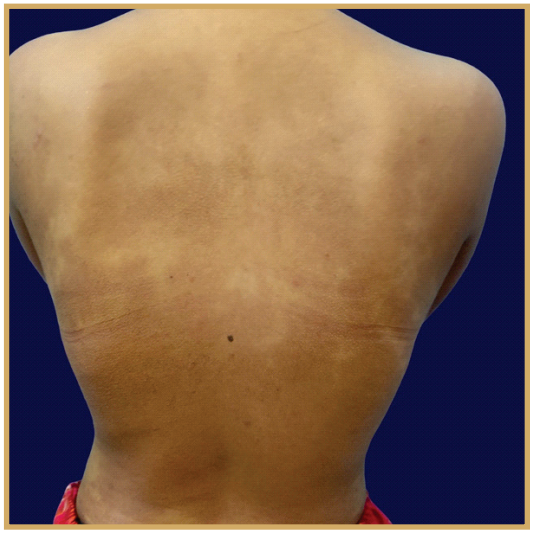

Fig. 4b

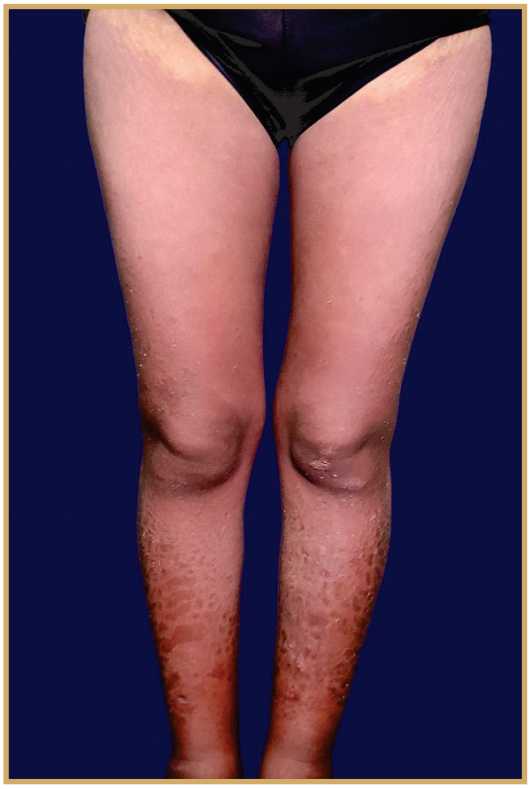

Fig. 4c

Figs. 4a, 4b, 4c (one-month post-treatment) : Erythematous plaques became less intense along with subsidence of most of erythematous papules over face, both upper limbs and lower limbs, breasts, lower abdomen and lower back. Ichthyotic changes are imperceptible over lower legs.

and foamy macrophages in the underlying dermis (Fig. 3). Fite Faraco stain was positive +4 (10-100 bacilli/field) in both histopathological samples. These features supported a diagnosis of borderline lepromatous leprosy. No histopathological findings of erythema nodosum leprosum were observed in the sections. A complete blood hemogram revealed low haemoglobin (7.1 g/dl), elevated total leukocyte counts (11,350 cells/cubic mm), neutrophilia (differential count: 80%), and reticulocytosis (8.36%). However, both the direct Coombs test and the indirect Coombs test were negative. Serum ferritin levels were high (394.5 ng/ml), while other parameters of the iron profile were within the normal range. Both C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR) were elevated (CRP: 105 mg/L, ESR: 56mm/hour). Serum vitamin B12 levels exceeded 2000 pg/ml. All tests for malaria, dengue, and chikungunya yielded negative results, while the anti-streptolysin O titre was elevated (ASO: 400 IU/ml). The blood culture result was negative. Antinuclear antibody (ANA), measured by immunofluorescence, exhibited a fine speckled pattern (++) with granular cytoplasmic staining (+) at a 1:100 dilution, and ANA profile analysis revealed positive Sm/RNP (Smith/Ribonucleoprotein) and SS-A (Systemic Sclerosis-A) antibodies. Rheumatoid factor (RA factor) was negative. Serum complement C3, IgG, IgA, and IgM levels were elevated (156.99 mg/dL, 2021.99 mg/dL, 473.15 mg/dL, and 277.31 mg/dL, respectively). Serum bilirubin and serum alkaline phosphatase levels were mildly elevated. All other parameters of serum biochemistry and urine analysis were within normal limits. Chest X-ray and X-rays of the hands and feet were normal. Abdominal ultrasonography revealed mild splenomegaly (size: 140 mm). Bilateral arteriovenous Doppler studies of upper limbs and lower limbs showed no abnormalities. Based on clinical history and positive investigative findings, we considered a diagnosis of borderline lepromatous leprosy, downgrading to lepromatous leprosy, with serological features of systemic lupus erythematosus (or Autoaggressive hanseniasis).

The patient was initiated on the World Health Organization (WHO) adult multibacillary treatment regimen, but dapsone was withheld until her haemoglobin level did not rise above 8 mg/dl with the support of haematinics. Additionally, the RO regimen (rifampicin 600 mg daily, and ofloxacin 400 mg daily) was added for a month to combat high bacillary load. To control the autoaggressive phenomenon, he was given a capsule of thalidomide 100 mg thrice daily for a month. Intravenous administration of 8 mg dexamethasone was provided each morning for a week, subsequently transitioning to oral prednisolone 30 mg in the morning for three weeks. Following one month of treatment, she exhibited significant symptomatic improvement, including resolution of fever, edema of the hands and feet, and an overall sense of well-being. Erythematous plaques, accompanied by background erythema, diminished in intensity, along with the subsidence of most superimposed papules on the face, back, abdomen, breast, and both upper and lower limbs (Figs. 4a, 4b, 4c). The patient is currently under our follow-up care and responding to treatment.

Discussion

The diverse clinical manifestations of leprosy render it a notable ‘chameleon’ within the medical field, often mimicking various illnesses, particularly connective tissue disorders. Regrettably, these resemblances occasionally cause physicians to overlook potential rheumatic symptoms, resulting in delayed diagnosis, when collateral damage has already taken

place. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease resulting from dysfunction in both innate and adaptive immunity, leading to uncontrolled production of auto antibodies and increased susceptibility to infections. *Mycobacterium leprae* could also serve as a trigger for lupus reactivation. Following uptake of *Mycobacterium lepra* bacilli, dendritic cells modulate inflammation through chemokine and cytokine production, thereby regulating adaptive cell-mediated immunity towards either a Th1 or Th2 response, which in turn leads to clinical manifestation (Cruz et al 2023). Numerous autoantibodies are observed as a result of aberrant humoral responses, with subsequent immune reactions stemming from these abnormalities. The multibacillary status of leprosy may serve as a potent trigger for immune complex production, although its association is not yet fully elucidated. Often, the sera of these patients show the presence of autoantibodies, potentially associated with i) molecular mimicry, ii) epitope sharing (shared epitopes between idiotypes from LL monoclonal antibodies (8E7 and TH9) and monoclonal antibodies from SLE patients), and iii) sustained cell damage leading to the release of sequestered antigens (Mackworth-Young et al 1987, Horta-Baas et al 2015).These factors could serve as triggers for the production of autoantibodies. Therefore, identifying rheumatic symptoms in leprosy is crucial, as they might be misinterpreted as systemic lupus erythematosus.

In 1987, Azulay coined the term “autoaggressive hanseniasis” (AH) based on the following clinical presentations and associated laboratory findings observed in multibacillary leprosy cases endemic to Brazil:

1. Prolonged fever (37°C-40°C) may persist for weeks or months, manifesting as occult fever with a relapsing and remitting course. Sometimes it is the first symptom to be experienced. Fever may be associated with constitutional symptoms like anorexia, weight loss, asthenia, and arthralgia.
2. Skin manifestations include malar rash, erythema multiforme, erythema nodosum, or necrotizing vasculitis-like lesions.
3. Extracutaneous lesions may be present in the form of generalized lymphadenopathy, arthritis, nephritis, orchitis, epididymitis, iritis, uveitis, and hepatitis.
4. High levels of immunoglobulins and complements are observed in the serum of these patients. In addition, one or more autoantibodies such as ANA, LE cell, RA factor, cryoprotein, and antithyroid antibodies are also present.
5. Presence of acid-fast bacilli (AFB) in slit-skin smears (SSS) or histopathologically confirmed cases of leprosy.

The presence of autoantibodies and high levels of immunoglobulins in patients with borderline leprosy and lepromatous leprosy, with or without reaction, had been reported in the literature even before the term AH was coined (Bonomo et al 1963, Bonomo et al 1965, Abe et al 1967, Lim & Fusaro 1968, Shwe 1972, Gupta et al 1978). Interestingly, these patients did not exhibit any clinical signs or symptoms associated with the presence of autoantibodies. Therefore, the significance of these autoantibodies remains elusive. Moreover, many of the afore mentioned clinical features are also present in type 2 lepra reactions (T2R), rendering it indistinguishable from autoaggressive hanseniasis. Following Azulay’s description of the term AH, there has been a paucity of published cases or literature featuring AH, except for one case report by Dhar et al in 1993.The only significant difference between T2R and AH appears to be the presence

of photosensitivity, malar rash, or erythema multiforme-like skin lesions, along with persistent fever in the latter. Thus, the status of AH as a distinct entity remains unsubstantiated in the absence of further studies.

In 2023, Youssef et al. reported a case initially misdiagnosed as mixed connective tissue disease, attributed to clinical manifestations such as lower leg vasculitis, non-healing ulcers, sclerotic skin changes, and supportive investigations revealing elevated levels of U1-ribonucleoprotein antibodies, RA factor, anticardiolipin immunoglobulin, and a positive ANA (1:160 dilution, speckled pattern) via hep-2 assay. However, upon inadequate response to hydroxychloroquine treatment, a repeat biopsy of the skin lesion confirmed the diagnosis of leprosy, prompting the initiation of anti-leprosy treatment.

Therefore, it is imperative to consider multibacillary leprosy as a potential differential diagnosis when an endemic patient presents with enduring rheumatic symptoms and autoimmune antibodies. Nevertheless, prior to confirming the diagnosis, it is essential to rule out SLE and other connective tissue diseases. Further, perplexing the distinction is the possibility that the patient may truly have both diseases simultaneously. At the moment, there is a paucity of published literature on how to distinguish between leprosy-induced SLE-like symptoms and true SLE.

The treatment of choice is thalidomide, administered at a dosage of 100 to 300 mg daily for several days (Azulay 1987). The second-choice drug is clofazimine, which is particularly recommended for female patients of reproductive age who are planning conception. In exceptional cases, corticosteroids may be considered. However, corticosteroids alone are not as effective as a combination of antileprosy treatment along with thalidomide or clofazimine.

Conclusion

In conclusion, our case highlights the diagnostic challenge posed by leprosy, which may mimic autoimmune connective tissue diseases. Physicians must remain vigilant in recognizing the rheumatic symptoms of leprosy and distinguishing them from other autoimmune conditions to ensure timely and appropriate management in a leprosy-endemic country like India. Thalidomide (or clofazimine), in combination with anti-leprosy treatment, emerged as an effective therapy for such patients.

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