Immunol Res (2015) 61:160–163
DOI 10.1007/s12026-014-8596-y

DIAGNOSTICS AND ENVIRONMENTAL FACTORS

Lupus and leprosy: beyond the coincidence

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Published online: 21 November 2014

Abstract Systemic lupus erythematous (SLE) is an autoimmune disease that presents an increased susceptibility to infections which may trigger reactivation. Disease flares have been mostly associated with parvovirus B19, cytomegalovirus, EBV and *Mycobacterium tuberculosis* infections, but it is probable that many other agents may also induce innate and adaptive immune system stimulation including the production of autoantibodies as ANA, anti nDNA and anti-ß2-GPI mainly in lepromatous leprosy. *Mycobacterium leprae* not only may determine symptoms that mimic lupus flares, including autoantibodies production, but could also act as a trigger for lupus reactivation; however, its association is still not fully explored. As demonstrated for tuberculosis, it is quite possible that molecular mimicry may also be involved in the interface of these two diseases. Some studies reported shared epitopes among idiotypes derived from 8E7 and TH9 lepromatous antibodies and those obtained from SLE patients, and it could partially explain the triggering phenomenon of SLE caused by *M. leprae*. We report and discuss three Brazilian patients whose disease was inactive and presented disease flares concurrently with the diagnosis of leprosy.

Keywords Systemic lupus erythematosus · Leprosy · Hansen disease

Introduction

Systemic lupus erythematous (SLE) is an autoimmune disease with multisystem involvement that typically intercalates periods of inflammatory activity with those of remissions. Primary dysfunction of the innate and the adaptive immunity contributes for the uncontrolled production of autoantibodies and its specific clinical manifestations. In addition, the immune derangements also increase susceptibility to infections, and microorganisms may act on its turn, as triggers for disease reactivation. Lupus flares have been reported to occur secondary to superimposed infections caused by Parvovirus B19 [1, 2], CMV [3, 4] and EBV [5]; furthermore, among fastidious pathogens, *M. tuberculosis* has been particularly associated with SLE flare triggering [6–8].

Besides tuberculosis, some other mycobacteria, as *Mycobacterium leprae*, may simultaneously occur in patients with SLE, and it may determine symptoms that mimic those of lupus, besides its stimulation for abnormal autoantibodies production [9, 10]. We herein present three Brazilian patients with a longstanding quiescent SLE, who had a concomitant diagnosis of leprosy and developed new lupus manifestations. The different aspects of the leprosy in the course of SLE are discussed.

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Case records

Case 1

WVM, a 31-year-old Afro-American man with SLE since 2002 was on use of azathioprine for lupus nephritis after an induction therapy with cyclophosphamide followed by mycophenolate mofetil. He presented no clinical signs of active disease but maintained a residual proteinuria. In 2006, he developed polyarthritis, fatigue and anorexia, and examination of the skin revealed plate-shaped, erythematous, hypoesthesic skin lesion with infiltrative borders on his right upper limb. A punch biopsy was performed and histopathological diagnosis of paucibacillary leprosy was confirmed. A multidrug therapy was started, and 4 weeks later, he still presented polyarthralgia and developed new palmoplantar vasculitis, malar rash and diffuse cutaneous mucinosis, with no bacilli at skin biopsy. A treatment with high doses of steroids had a satisfactory response. Over the six-month therapy, he also experimented a type I reaction that was successfully treated with steroids. Currently, he is on SLE remission and has no signs of active leprosy.

Case 2

SG, a 41-year-old Afro-American woman with a longstanding SLE including nephritis has been successfully treated with steroids, cyclophosphamide and azathioprine. She also presented a metabolic syndrome and was under low doses of prednisone. In October 2012, after 12 years of lupus remission, she developed disseminated erythematous, pruritic papules and a skin biopsy confirmed lepromatous leprosy (LL) with a positive acid-fast bacilli (AFB) smear so that polychemotherapy was started. Five months later, she was hospitalized with fever, polyarthralgia, diffuse mucinosis and multiple cutaneous abscesses with AFB positive smear. Complementary investigation unveiled a haemolytic anaemia, and she was successfully treated with hydroxychloroquine and high doses of prednisone which were subsequently titrated.

Case 3

ASM, a 42-year-old Afro-American female was diagnosed with SLE in 2010 due to glomerulonephritis associated with low complement serum levels and high titles of nuclear ANA. After a longstanding SLE remission, she experienced a nephritic flare and was treated with steroids and cyclophosphamide. During the induction therapy, she developed an erythematous, hypoesthesic cutaneous lesion on her right arm and bilateral ulnar neuritis. A skin biopsy confirmed the clinical hypothesis of leprosy, and she was treated with polychemotherapy. Six months later she achieved resolution of cutaneous lesions but only partial response of the lupus nephritis.

Discussion

We herein report three patients with SLE who presented active lupus manifestations coincidentally with leprosy diagnosis. We emphasize the fact that all three patients were in sustained remission until the infection occurred and that all lupus symptoms subsided after leprosy therapy.

Leprosy, or Hansen's disease, is a chronic mycobacterial infection that affects the skin and peripheral nerves [11]. It is caused by *M. leprae*, an acid-alcohol-fast obligate intracellular bacillus with a tropism for reticuloendothelial cells and peripheral nerves. Most cases occur in tropical countries mainly India and Brazil according to WHO report [12]. Its clinical manifestations are variable and encompass a wide spectrum of symptoms depending upon host immune response as the tuberculoid pole (TT) implies an organized cellular response with few bacilli, antagonistically to the absence of specific immune response and a high burden of microorganisms seen at the LL [11, 13].

After bacilli uptake, dendritic cells modulate inflammation with production of cytokines and chemokines and regulate the adaptive cell-mediated immunity into a Th1 or Th2 response [14, 15]. The ability of *M. leprae* to regulate cytokine production and to drive Th-1 or Th-2 responses may contribute to clinical presentation [16].

These immune abnormalities are also responsible for acute reactions that may occur in any moment of the infection: type 1, reversal reaction and type 2, erythema nodosum leprosum. Although the mechanisms of these reactions are not well understood, many of the clinical manifestations may mimic rheumatic diseases [14, 17, 18]. Frequently, leprosy patients exhibit symmetrical polyarthritis with puffy hands and feet, dactylitis and chronic erosive arthritis. Besides osteoarticular symptoms, leprosy has been associated with orchitis, mononeuritis multiplex, lymphadenopathy, serositis, uveitis, necrotizing vasculitis, haemolytic anaemia, alopecia, photosensitivity, glomerulonephritis and many skin lesions including the rare and severe Lucio's phenomenon that leads to purpura fulminans [14, 17–19]. All of the above could be explained by a primary systemic vasculitis or a collagen vascular disease like SLE [19, 20].

Aberrant humoral response can also be expressed by the presence of many autoantibodies. The prevalence of rheumatoid factor (RF) and antinuclear antibodies (ANA) varies among different studies but is more common in lepromatous pole [21]. At this scenario, the multibacillary status may exert a potent trigger for immune complex production. ANA positivity may reach 30 %, and one study

described similar prevalence of anti-ssDNA antibodies between SLE and leprosy patients [22–25]. Antiphospholipid antibodies (aPL) are also reported in multibacillary leprosy sera in up to 98 % [26–30]. A Brazilian study demonstrated a high prevalence of some of the new SLE criteria in one hundred LL patients, especially malar rash (44 %), arthritis (23 %) and positive aPL (20 %) [20]. However, another Brazilian study showed that more specific autoantibodies, such as anti-dsDNA, anti-Sm and anti-P, are infrequently found in leprosy sera [31]. ANA positivity may be related to weak cross-reactivity between mycobacterial antigens and human DNA associated with continuous stimulation of B cells due to cell destruction [32].

Anti-ß2-glycoprotein 1 (anti-ß2-GPI) antibodies have also been described in serum of leprosy patients, but many studies reported heterogeneity of ß2-GPI dependence aPL in leprosy [32–34]. One study demonstrated higher prevalence of aPL and anti-ß2-GPI in LL than healthy controls, but despite being ß2-GPI dependent, no thrombotic manifestations were demonstrated [34]. On the other hand, Lucio's phenomenon is characterized by microangiopathic thrombosis [33]. Indeed, it has been shown that infections may trigger thrombotic complications, as a "second hit". The molecular mimicry phenomenon contribution is supported by the evidence of shared sequence of peptides between some microorganisms and ß2-GPI binding site of anticardiolipin [35].

In addition to the clinical and autoantibody production similarities, the interface between mycobacterial infections and lupus may be more extensive. The role of tuberculosis as a possible trigger for lupus flare is well known [6, 36], but little is said about leprosy. Shared epitopes between *M. tuberculosis* and self-antigens, such as DNA, have been demonstrated [37–39]. Curiously, our three patients were under sustained remission until appearance of new lesions due to leprosy. It is quite possible that molecular mimicry may also be involved in the interface SLE–leprosy. Some studies have reported shared epitopes between idiotypes from LL monoclonal antibodies (8E7 and TH9) and monoclonal antibodies from SLE patients [40–42]. These data may suggest that a subset of B cells in both diseases encoded immunoglobulin variable region genes. It could explain several similarities between SLE and this intriguing infectious disease and why our patients only went into remission again after treatment of leprosy.

In conclusion, although the role of *M. leprae* in the SLE pathogenesis is not established, this agent should always be remembered as a trigger for lupus flares, especially in endemic regions.

Conflict of interest None.

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