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Lepromatous Leprosy Mimicking Systemic Lupus Erythematosus

A Clinical Pathology Conference Held by the Division of Rheumatology at Hospital for Special Surgery

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Case Presentation

A 29-year-old Brazilian woman was referred for management of systemic lupus erythematosus (SLE) with antiphospholipid antibodies (aPL). Her symptoms were 1 year of intermittent fever and diffuse, tender, erythematosus, and nodular rash that began during her first pregnancy. She was treated with short course of low-dose corticosteroids, with resolution; however, she suffered an embryonic loss at 7 weeks. Six months prior to admission, she had recurrence of the nodular rash with new onset arthralgia; a skin biopsy showed panniculitis. Tests done at that time showed lupus anticoagulant (LA), anticardiolipin antibody (aCL) IgM >150 U (normal 0–7 U), anti-β_2 glycoprotein-I (aβ_2GPI) IgM >150 U (normal <10 U), and aβ_2GPI IgA of 135 U/mL (normal <10 U), the other isotypes being negative. For the presumed diagnosis of a "systemic lupus erythematous (SLE)-like autoimmune disease," she was prescribed hydroxychloroquine (HCQ) 300 mg daily and prednisone 10 mg twice a day with significant response. However, her nodules recurred in 1 month when her prednisone dose was tapered to 15 mg daily, and azathioprine 100 mg daily and dapsone 25 mg daily were begun.

Four months prior to admission, her rash and fever worsened. Prednisone was increased to 60 mg a day with no improvement. Three months prior to admission, she developed symmetric polyarthritis of metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs), wrists, knees, and ankles. Prednisone was increased to 120 mg daily and her azathioprine was switched to mycophenolate mofetil (MMF) 3.0 g daily with improvement. Two months prior to admission, she was started on enoxaparin sodium subcutaneously 50 mg twice daily. One month prior to admission, MMF was stopped and dapsone dose was increased to 50 mg daily.

Despite the above management, her condition worsened. When she was admitted, she had diffuse erythematous papules and nodules over her extremities, abdomen, chest, back, and face. She denied weight loss, night sweats, alopecia, photosensitivity, oral ulcers, sicca symptoms, Raynaud's phenomenon, chest pain, shortness of breath, cough, nausea and vomiting, abdominal pain, dysuria, hematuria, arthritis, arthralgia, and myalgia. She had no history of thrombosis. She had no recent travel history and had emigrated from

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rural Brazil several years prior to presentation. She denied any alcohol, tobacco, illicit drug use, or new medications. She had Bacillus Calmette–Guérin (BCG) vaccine as a child and had no drug allergies.

On admission, her medications were HCQ 200 mg twice daily, prednisone 20 mg daily, enoxaparin sodium 50 mg twice daily, calcium, vitamin D, and acetylsalicylic acid 325 mg daily. On physical examination, the patient had a temperature of 39.5°C, heart rate 120 beats per minute, blood pressure 120/70 mmHg, and oxygen saturation 100% on room air. She was not ill appearing but had cushingoid features. She had no cervical lymphadenopathy. She had no lower extremity edema, synovitis, or joint tenderness. Skin examination showed livedo reticularis and edematous indurated erythematous papules on her cheeks, forehead, right earlobe, chest, abdomen, and extremities (Figs. 1 and 2). There was no mucosal involvement. The remainder of the examination was normal.

Laboratory evaluation showed marked leukocytosis and mild anemia. Her partial thromboplastin time (PTT) was slightly elevated and she was hypoalbuminemic. She had negative lupus serologies, normal complement levels, and triple aPL-positivity (Table 1). A repeat skin biopsy was performed.

Discussion—Pathology

The first outside biopsy, which showed inflammatory changes in the subcutaneous fat consistent with *panniculitis* was not available for our review. There was no special staining performed in this specimen.

The second punch skin biopsy, which was performed at our center, consisted of three fragments (epidermis, dermis, and subcutis), which showed collections of lipidized macrophages with the dermis and subcutaneous fat with a minimal accompanying lymphocytic and neutrophilic infiltrate (Figs. 3 and 4). The zones of lipophage accumulation were modest and exhibited perivascular accentuation. The specimen showed lobular panniculitis, which was composed of aggregates of histiocytes mixed with rare lymphocytes. The cytomorphology of these histiocytes was characteristic for lepromatous leprosy representing the Virchow's histiocyte characterized by mononuclear cells with abundant granular and vacuolated cytoplasm (Fig. 4).

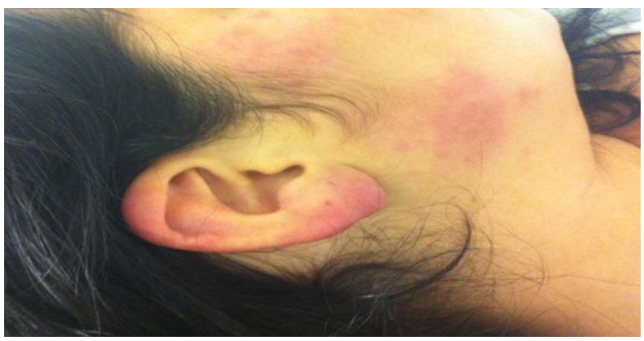

Fig. 1. Diffuse maculopapular erythematous lesions on the face and earlobe.

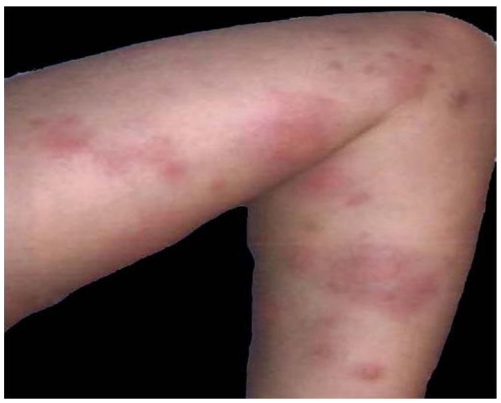

Fig. 2. Diffuse indurated erythematous maculopapular rash on the left arm.

The specimen was stained with a Fite's preparation, a new fuchsin-formaldehyde acid-fast bacilli (AFB) stain for lepra bacilli. At higher magnification, the Fite's stain showed numerous acid-fast positive bacilli within the macrophages (Fig. 5). Well-formed cohesive epithelioid granuloma typical of tuberculoid leprosy was not seen.

Overall these findings were diagnostic of lepromatous leprosy (histiocytoid leprosy) with a minimal adaptive immune response. The clinical presentation along with the morphology captured on this biopsy was typical for lepromatous leprosy.

It is likely that the patient's immunosuppressive therapy resulted in attenuation of the immune response, hence allowing a dysregulated and excessive proliferation of lipid wall containing lepromatous bacilli within scavenger macrophages. These findings were not consistent with any of the lepra reactions. In erythema nodosum leprosum, an Arthus' type 3 immune complex reaction comprising antibody bound to sterile bacterial antigens is manifested morphologically as a leukocytoclastic vasculitis, which was not identified in this case. While there was infiltration of vessel wall, a finding seen in Lucio's phenomenon, there were no supervening inflammatory, septic, or vasculitic changes.

Table 1 Laboratory tests

Value	Admission	Reference range
White blood cell	27.9	3.4–11.2 K/μL
Neutrophils	93.5	45–75%
Hemoglobin	10.5	11.7–16.0 g/dL
Platelets	247	150–450 K/μL
Prothrombin time	16.1	9.4–11.5 s
Partial thromboplastin time	60	25.0–35.0 s
Antinuclear antibody	Negative	Negative
Anti-dsDNA antibody	Negative	Negative
Lupus anticoagulant test	1.89	0–1.29 ratio
Anti-β_2 glycoprotein I IgM	150	<10.0 U/mL
Anti-β_2 glycoprotein-I IgA	91	<10.0 U/mL
Anti-β_2 glycoprotein I IgG	5	<10.0 U/mL
Anticardiolipin IgG	2	0–14 units
Anticardiolipin IgM	80	0–7 units
Anticardiolipin IgA	39	0–14 units
Complement 3	95	85.0–193.0 mg/dL
Complement 4	20	12.0–36.0 mg/dL

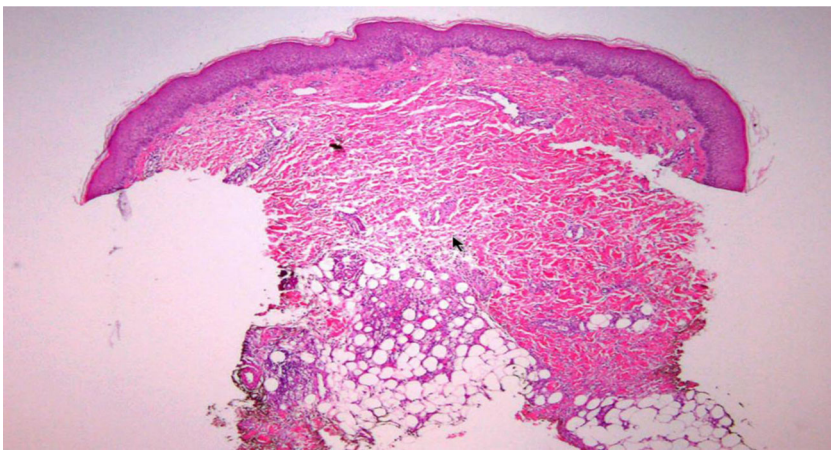

Fig. 3. The skin biopsy shows lipidized macrophages with the dermis and subcutaneous fat with a minimal accompanying lymphocytic and neutrophilic infiltrate.

Of note, panniculitis in the form of erythematous and nodular rash is relatively common in leprosy, occurring in approximately 50% of patients with lepromatous leprosy, and it reflects a type 2 immunologic reaction (further discussed below) that manifests as eruption of subcutaneous nodules usually in the deep dermis.

Discussion—Rheumatology

The patient is a 29-year-old Brazilian woman with persistently positive aPL presenting with 1 year of intermittent fever and diffuse tender erythematous nodular rash, which was diagnosed by skin biopsy as lepromatous leprosy.

Leprosy, also known as Hansen's disease, caused by *Mycobacterium leprae* is an infectious disease preferentially involving the skin and the peripheral nervous system. Brazil is the second in the world in number of cases of leprosy after India. In the Americas, 93% of the reported cases are from Brazil. Leprosy is more common in men than in women, at a ratio of 1.5 to 1. The mode of disease transmission is not clear; it is assumed that leprosy mostly spreads by respiratory system or through broken skin; the bacterium has been found in secretions; a long-lasting contact seems to be necessary for transmission [1].

There are four clinical forms of leprosy: indeterminate (early), tuberculoid, dimorphic, and lepromatous (Virchowian). The first two are paucibacillary and the latter two are multibacillary [17, 19]. The clinical presentation of leprosy is variable including erythema nodosum, arthritis, fever, skin erythema, vasculitis, epididymitis, glomerulonephritis, pericarditis, and pleurisy [17, 19]. Osteoarticular involvement is third most common after the skin and peripheral nervous system manifestations [21]. Lepromatous leprosy causes madarosis (loss of the eyebrows), swelling of the cheeks and earlobes, and disseminated skin nodules on the face that can ulcerate resulting in irreversible damage. The diagnosis is established based on full-depth skin or nerve biopsy smears demonstrating AFB.

Because of diverse clinical manifestations (e.g., dermatological, neurological), leprosy can be confused with other systemic autoimmune diseases including SLE. Thus, physicians should consider leprosy in the differential diagnosis of SLE and/or antiphospholipid syndrome (APS) with unusual

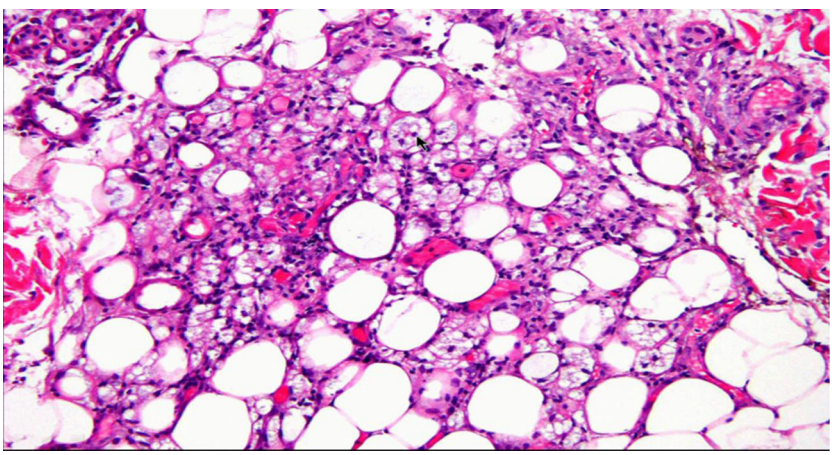

Fig. 4. Panniculitis is composed of aggregates of histiocytes with granular cytoplasm called Virchow cells—the hallmark of lepromatous leprosy mixed with rare lymphocytes.

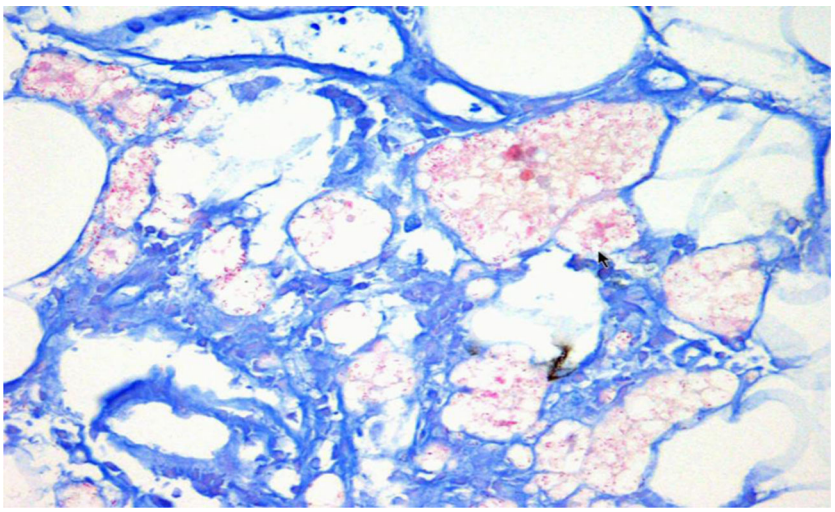

Fig. 5. Fite stain showing bacilli within the vacuolated macrophages.

presentations, especially in endemic areas for leprosy, and order targeted biopsies. Patients can have malar rash, arthritis, photosensitivity, as well as the autoantibodies that can occur in lupus patients [23]. Joint involvement, mimicking rheumatoid arthritis, can also occur in leprosy. A variety of autoantibodies can be detected in leprosy patients such as double-stranded DNA (anti-dsDNA), anti-mitochondrial antibodies (AMA), and aPL [11, 12]. American College of Rheumatology (ACR) lupus classification criteria, which shows sensitivity and specificity of 96 and 84%, respectively, has 16% false-positive rate for lupus among Brazilian leprosy patients [23].

If therapy for leprosy is delayed, nonreversible damage of the eyes, hands, and feet can occur due to neuropathy [5]. The World Health Organization (WHO) suggests that leprosy should be treated with multiple drug therapy (MDT) to avoid drug resistance. Paucibacillary leprosy should be treated with dapsone and rifampin for 6 months, whereas multibacillary leprosy with dapsone, rifampin, and clofazimine for a year. Other antibiotics like clarithromycin, fluoroquinolones, and minocycline can be used for patients with recurrent disease or for patients who have intolerance to the standard therapy.

Thalidomide, which is used for discoid lupus and myeloma, is also Food and Drug Administration (FDA) approved for erythema nodosum leprosy. This medication is a paradox for rheumatologists because it can induce thrombosis [22], a special concern for aPL-positive patients. It is not clear from the few case reports that if thalidomide induces thrombosis through aPL production or other mechanisms. Some suggest that patients on thalidomide should be anticoagulated or receive low-dose ASA [20].

Bacillus Calmette–Guérin immunization can bolster the immune response in those exposed to leprosy by activating the innate immune response and increasing production of cytokines such as tissue necrosis factor (TNF)-alpha. Thus, there is probably some degree of protection against leprosy in people who have received neonatal BCG vaccination for tuberculosis prevention. As with tuberculosis, the degree of protection conferred by BCG against leprosy should vary from host to host; the reasons for this variability remains unknown.

Discussion—the Association Between Leprosy and Antiphospholipid Antibodies

In the early 1990s, β_2GPI was discovered as the cofactor for autoimmune aCL as well as the main target antigen for aPL [10]. Early considerations suggested two types of aPL: autoimmune (aβ_2GPI-dependent), and alloimmune or infectious (aβ_2GPI-independent), but this conclusion is currently questioned. β_2GPI-dependent aCL can rarely occur in some infections, including leprosy [2, 8–10, 13, 16, 18].

The prevalence of aPL in leprosy is highly variable; aCL reported in 20–98% and aβ_2GPI in 3–89% of patients [2, 4, 8, 9, 13, 14]. Although IgM is the most common aCL isotype, IgG isotype also occurs, mostly in the lepromatous form [7]. The wide prevalence range of aPL in leprosy patients may be explained by the fact that infection-induced aPL are usually transient, but some leprosy patients develop persistent, possibly autoimmune, aPL.

Lucio's phenomenon is a rare necrotizing skin lesion of leprosy described initially in Mexico. Patients with Lucio's phenomenon develop small vessel thrombosis similar to that seen in APS patients [24]. Biopsies show microthrombosis without inflammation as the abundant bacilli are thought to cause microthrombosis by endothelial proliferation and occlusion. Surprisingly, such patients have aβ_2GPI-dependent autoimmune aPL [15]. Furthermore, Brazilian leprosy patients with Lucio's phenomenon, compared to those without, more commonly fulfill the updated Sapporo Classification Criteria for APS [3].

It is unknown why some leprosy patients develop β_2GPI-dependent and others β_2GPI-independent aPL.

β_2 glycoprotein-I is a single chain glycoprotein consisting of five domains, with domain V binding to phospholipids. It binds to receptors as a dimmer. Mutation of a domain V gene that exchanges leucine for valine at position 247 (val247leu in place of val247val) causes structural modification in the protein. A recent study concluded that leprosy patients homozygous for val247val have a greater tendency to produce the pathogenic β_2GPI-dependent aPL [6].

Leprosy patients may develop a wide spectrum of clinical and laboratory manifestations because of different immunological responses: (a) type 1, seen mostly in tuberculoid leprosy (mild clinical presentation mostly with IgM aCL), represents a slight increase in cell-mediated immunity; and (b) type 2, mostly in lepromatous leprosy (severe clinical presentation mostly with IgG aCL), causes an antigen-antibody complex-mediated immune complex disease with complement activation, the morphologic expression of which is leukocytoclastic vasculitis with expression of TNF-α and interferon-γ [14].

Hospital Course

We speculate that the patient's clinical worsening on low-dose (25–50 mg daily) dapsone before the leprosy diagnosis was related to her profound concurrent immunosuppressive treatment. Following the diagnosis, the patient's dapsone dose was increased to 100 mg oral daily, and clofazimine 100 mg oral daily and rifampin 600 mg oral daily were added. She showed steady improvement of the next several months, at which time she returned to Brazil and was lost to follow-up.

Conclusion

Leprosy mimics systemic autoimmune diseases, mainly lupus. In patients from geographic areas in which leprosy is prevalent, leprosy must be included in the differential diagnosis of patients with SLE-like systemic autoimmune diseases and/or aPL with atypical features. Leprosy patients can fulfill the classification criteria for lupus and antiphospholipid syndrome.

Disclosures

Conflict of Interest: Asli Karadeniz, MD, Lindsay Lally, MD, Cynthia Magro, MD, Doruk Erkan, MD, and Michael D. Lockshin, MD have declared that they have no conflict of interest. Roger Levy, MD reports personal fees and non-financial support from Abbvie and Janssen, personal fees from GSK, Roche, and Pfizer, outside the submitted work.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent: Informed consent was waived from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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