Lepromatous Leprosy with Erythema Nodosum Leprosum Presenting as Chronic Ulcers with Vasculitis: A Case Report and Discussion

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Abstract
Leprosy is a rare, chronic, granulomatous infectious disease with cutaneous and neurologic sequelae. It can be a challenging differential diagnosis in dermatology practice due to several overlapping features with rheumatologic disorders. Patients with leprosy can develop reactive states as a result of immune complex-mediated inflammatory processes, leading to the appearance of additional cutaneous lesions that may further complicate the clinical picture. We describe a case of a woman presenting with a long history of a recurrent bullous rash with chronic ulcers, with an evolution of vasculitic diagnoses, who was later determined to have lepromatous leprosy with reactive erythema nodosum leprosum (ENL).

Introduction
Leprosy is a slowly progressive disease caused by infection with Mycobacterium leprae (M. leprae). Spread continues at a steady rate in several endemic countries, with more than 200,000 new cases reported globally each year.1 Transmission occurs through nasal or oral droplets in a susceptible person.2 Organisms mainly infect the skin, peripheral nerves, mucosal surfaces of the upper respiratory tract, and eyes. The clinical severity of leprosy is dependent on the affected individual’s degree of immunity to M. leprae, as it is hypothesized that most immunocompetent people in endemic areas have mounted an immune response against it.3,4 Sequelae of this disease include deformity of the extremities due to complications of neuropathy.2 If diagnosed in a timely manner, leprosy can be effectively cured with multidrug therapy before disability develops.

ENL, a type 2 leprosy reaction, is a severe multi-system immune-mediated complication of lepromatous leprosy and borderline leprosy that causes patients to become acutely ill with fever, malaise, and tender erythematous skin lesions.5 It affects approximately half of lepromatous leprosy cases, can involve many organ systems, and can be recurrent. ENL typically occurs in lepromatous patients with abundant bacilli in cutaneous and peripheral nerve lesions within a few years of initiating antibiotic treatment for leprosy.4 The pathophysiology has not been fully elucidated but is thought to be due to cellular immunity mechanisms and antigen-antibody immune-complex deposition in vascular endothelium.4

Case Report
A 62-year-old Hispanic woman presented to the emergency department with nausea and vomiting. Her past medical history was significant for recurrent bilateral lower-extremity ulcers, which she had been battling for seven years. The ulcers began as blisters on bilateral thighs. Initial cutaneous biopsy revealed features of leukocytoclastic vasculitis and panniculitis. She was treated with a short course of prednisone, and the blisters improved. In subsequent years, the rash relapsed several times, and a full rheumatologic evaluation led to the diagnosis of cutaneous cryoglobulinemic vasculitis. The patient started rituximab infusions, which were discontinued after 18 months because of worsening lower-extremity ulcerating wounds. She eventually developed a secondary lower-extremity cellulitis accompanied by an intense bullous purpuric rash on bilateral arms and face. For these complaints she was seen in a Complex Medical Dermatology Clinic and clinically diagnosed with cutaneous polyarteritis nodosa. The patient declined recommendations for further immunosuppressive therapies. The rash on her arms and face ultimately resolved without treatment. She began attending a weekly wound clinic for her chronic lower-extremity ulcers.

Other past medical history included type 2 diabetes mellitus, peripheral neuropathy, arthritis, chronic sinusitis, and bilateral iritis. The patient was born in Mexico and moved to northern California in 1994. There was no recent travel, and she last visited Mexico 10 years prior.

On examination, the patient was febrile, hypotensive, tachycardic, and tachypneic. Her bilateral lower extremities had multiple ulcerative lesions ranging from 1 cm to 5 cm, with purulent drainage and surrounding erythema (Figures 1, 2). Surrounding skin was warm and dry, with areas of scarring and scaling. Interestingly, it was noted that the patient’s eyebrows were lacking hair bilaterally. Laboratory studies showed leukocytosis, anemia, and lactic acidosis. The patient was admitted for management of sepsis secondary to bacteremia, with lower-extremity cellulitis as the suspected source. A skin biopsy was taken from the left thigh, and histopathology showed epidermal ulceration with underlying septal and lobular panniculitis (Figure 3). A skin culture was positive for moderate growth of Staphylococcus aureus (S. aureus). A skin smear revealed many acid-fast bacilli (AFB), and an AFB stain was positive for numerous organisms within the subcutis and dermis (Figure 4).

On hospital day three, the patient developed a palpable purpuric rash on bilateral upper extremities, trunk, and face, which subsequently became edematous and formed confluent flaccid bullae (Figure 5). The rash was non-tender and non-pruritic. It was similar to her past widespread rash. A skin biopsy was taken from the left arm, revealing leukocytoclastic vasculitis (Figure 6). The AFB smear and stain were again positive for...
numerous AFB organisms (Figure 7). The patient’s bacteremia and cellulitis resolved with 14 days of intravenous vancomycin treatment. The purpuric rash evolved into confluent erosions and ulcerations by the day of discharge (Figure 8).

Both skin biopsies obtained during this hospitalization were sent to the National Hansen’s Disease Laboratory for further evaluation with Fite stain and PCR testing for M. leprae DNA. The thigh skin biopsy (hospital day one) revealed chronic inflammatory infiltrate and numerous acid-fast organisms within histiocytes and endothelial cells, consistent with lepromatous leprosy. The arm skin biopsy (hospital day three) was significant for acute and chronic inflammatory infiltrate, vasculitis, fibrin clots in blood vessels, and acid-fast organisms within histiocytes and endothelial cells, indicative of reactional ENL. Polymerase chain reaction (PCR) was positive for M. leprae DNA, confirming the diagnosis of active lepromatous leprosy.

The patient was subsequently referred to the National Hansen’s Disease Ambulatory Care Clinic in California for initiation of treatment. She was started on dapsone 100 mg daily, rifampin 300 mg monthly, and clofazimine 50 mg daily plus an additional 300 mg once a month. She was also started on a prednisone taper for one month and thalidomide 300 mg daily for treatment of the erythema nodosum leprosum reaction. The patient demonstrated expeditious response to treatment. Within six weeks, almost all of her skin lesions had healed with residual hyperpigmented scar tissue and scattered eschar (Figures 9, 10). She reported feeling better than she had felt in years.

**Discussion**

The clinical manifestations of leprosy depend on the host response to M. leprae. Therefore, lepromatous disease can present with a multitude of symptoms ranging from skin lesions to nerve damage. For this reason, diagnosis can be challenging. In non-endemic countries, the diagnosis of leprosy is frequently delayed, and patients may present to a variety of specialists for help. In the United States, where there are approximately 200 reported leprosy cases per year, one study found that leprosy patients experienced an average of one year of symptomatic illness before diagnosis was made. Patients with leprosy have been most commonly misdiagnosed with diabetic neuropathy, Lyme disease, lupus vulgaris, and numerous rheumatologic diseases.

Leprosy shares several common features with chronic inflammatory rheumatologic disease and can be a challenging mimicker to expose. Autoantibodies such as rheumatoid factor and anti-nuclear antibody are often falsely positive in leprosy. The patient in our case underwent extensive rheumatologic evaluation and was diagnosed initially with cryoglobulinemia vasculitis, then polyarteritis nodosa. However, her skin lesions progressively worsened on rituximab immunosuppressive therapy due to the underlying undiagnosed infection.

The positive AFB smear obtained during hospitalization widened the differential diagnosis to include cutaneous infections caused by mycobacterial pathogens, including erythema induratum (M. tuberculosis or M. bovis), Buruli ulcer (M. ulcerans) and lepromatous leprosy or erythema nodosum leprosum (M. leprae). The

**Figure 7. AFB (100x): Biopsy of left arm exhibiting M. leprae organisms in the cell wall.**

**Figure 8. Large confluent ulcerations on the arm six weeks after eruption of the second purpuric rash on the upper extremities and face.**

**Figure 9. Leg lesion after six weeks of multi-drug treatment, with healed scars and residual hyperpigmentation.**

**Figure 10. Arm lesion six weeks after multi-drug treatment, with healed scars and minimal scattered eschar.**
on the presence of one or more of the cardinal signs: hypopigmented or reddish patches with definite loss of sensation, thickened peripheral nerves, and AFB on skin smears or biopsy.2 The skin lesions are commonly macules or plaques and seldom papules or nodules.3 Our patient’s presentation was atypical in that her skin lesions had formed chronic, non-healing ulcers as a result of the prolonged duration of her untreated disease and her comorbid diabetes mellitus, which likely contributed to her impaired wound healing and the recurrent infection of chronic wounds.13

The biopsy from the purpuric rash that developed acutely on hospital day three was histologically consistent with ENL. ENL is distinguished by acutely on hospital day three was histologically consistent with ENL. ENL is distinguished by intense perivascular infiltrates of neutrophils throughout the dermis and subcutis.3 Other characteristic histological features include tissue edema, inflammatory infiltrates, vasculitis, necrotizing changes and thrombus formation within vessels.13 The appearance of ENL is classically described as crops of tender subcutaneous nodules on the face and outer surfaces of limbs.7 Our patient had purpuric, bullous lesions on her face and arms. Atypical presentations of ENL, documented in case reports from high-endemic countries such as Mexico and India, include bullous, ulcerated, pustular, and erythema multiforme-like lesions.14,15 ENL can present as inflammation affecting multiple systems, causing iritis, neuritis, myositis, lymphadenitis, and arthritis.16 It may occur as a single acute episode or have a protracted relapsing course lasting several years.16 Our patient had a history of iritis and arthritis, which may have been the sequelae of recurrent ENL. Similarly, her prior diagnoses of peripheral neuropathy and chronic sinusitis were likely manifestations of lepromatous disease.

First-line treatment for ENL is immunosuppression with corticosteroids.1 Another highly effective agent is thalidomide, which treats the acute inflammation and maintains long-term immunosuppression with few side effects.3

Conclusion

Leprosy can be difficult to diagnose in regions where the prevalence is low. For patients from endemic countries, it is important to place the diagnosis high on one’s differential. Because the incubation period of leprosy averages four years to ten years, patients can present with leprosy long after leaving an endemic area.17 Early diagnosis and treatment of leprosy and lepromatous reactions is essential for minimizing nerve damage, preventing disability, and effectively curing the disease. Neuropathic impairment and morbidity worsens with delayed time to diagnosis, resulting in complications such as contractures and secondary damage to neuropathic areas.16 Diagnosing leprosy thus requires a high index of clinical suspicion and astute clinical judgment. This uncommon but debilitating disease should remain in consideration in the differential diagnosis of a patient presenting with chronic dermatitis and neuropathy, even in non-endemic regions.

References

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