


Persistent Infection Versus Type 2 Immunological Reaction in Lepromatous Leprosy

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Abstract

The distinction between persistent infection and immunologic reactions in leprosy is often difficult but critically important since their management is different. We present the case of a 51-year-old Vietnamese female who presented in 2015 with areas of erythema and skin infiltration on face and chest, as well as edema on her hands and feet. Skin biopsy was consistent with lepromatous leprosy. She was treated with rifampin, clarithromycin, and levofloxacin for 2 years. Her lower extremity edema was attributed to type 2 immunological reaction for which she was started on prednisone and methotrexate, but she was lost to follow-up for 19 months. She presented with new skin lesions and pain on her extremities. New biopsies revealed an intense neutrophilic infiltrate in the dermis and acid-fast bacilli focally within cutaneous nerve twigs. As compared with the initial biopsy, the inflammatory infiltrates were diminished and the bacilli had a degenerating appearance. These findings were consistent with type 2 immunological reaction. The patient was treated with thalidomide with improvement in the appearance of the skin lesions. A follow-up biopsy showed lack of neutrophilic infiltrates and decreased number of bacilli. This case illustrates the importance of differentiating between persistent infection and immunologic reactions in leprosy. Clinicians should be aware of these complications. A high index of suspicion and accurate interpretation of skin biopsy results are essential for appropriate diagnosis.

Keywords

leprosy, *Mycobacterium leprae*, type 2 immunological reaction, erythema nodosum leprosum

Introduction

Leprosy is a deforming disease that affects nerves, skin, eyes, and facial mucosa. The disease is caused by *Mycobacterium leprae* and *M lepromatosis*. Clinical presentation is based on the host's immune response.¹ Distinction between persistent infection and immunologic reactions in leprosy is often difficult but critically important since their management is different. Persistent infection often reflects poor adherence to antimycobacterial treatment. Mechanisms leading to immunological reactions are poorly understood, clinical presentation is nonspecific, and treatment is not standardized. We present a case of previously treated lepromatous leprosy who presented with a type 2 immunological reaction (T2R). Diagnostic and management considerations are discussed.

Case Report

A 51-year-old Vietnamese female, who migrated to the United States at age 25 years, was seen at an outside clinic in East Texas in 2015. She had a 1-year history of lesions consistent with areas of erythema and infiltration of dermis of

the cheeks, chin, nose, and chest. She reported numbness, weakness, and edema of her hands and feet for 4 months. Skin biopsy of the left ear showed chronic inflammatory infiltrates replacing 75% of dermis but separated from the basal layer of the epidermis by a clear zone. The infiltrates were composed of foamy histiocytes and lymphocytes involving cutaneous nerves. Fite stain revealed numerous acid-fast bacilli within histiocytes and cutaneous nerves. She was diagnosed with lepromatous leprosy. The treatment consisted of rifampin 600 mg daily (eventually monthly), clarithromycin 500 mg daily, and levofloxacin 500 mg daily for

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Figure 1. Image of the anterior forearms. Multiple nodules on anterior forearms, hypotrichosis, and areas of hyperpigmentation. Some lesions had inflammatory appearance, which are typical for active lesions in the setting of erythema nodosum leprosum.

2 years. Dapsone and minocycline were also prescribed but discontinued due to adverse effects (hemolytic anemia and hyperpigmentation, respectively). She did not receive clofazimine due to prior hyperpigmentation. Her extremity edema was attributed to T2R; however, edema is also an identified feature of lepromatous leprosy. Treatment with prednisone and eventually methotrexate was started but she was lost to follow-up for 19 months before reestablishing care at our institution.

She presented with new indurated tender skin lesions and worsening pain and edema on her extremities, since last seen. She also reported subjective fever and weight loss (30 lbs in 4 months). On physical examination, she had extensive erythematous subcutaneous papules and nodules with a background of gray hyperpigmentation on her arms and legs (Figure 1), and few scattered tender superficial erythematous nodules on the face and abdomen. Madarosis and hypotrichosis of arms and legs were seen. Decreased light touch (monofilament 0.2 gr) in the left arm and loss of protective pain sensation (10 gr monofilament) in both feet with glove-stocking pattern were noted. The remainder of her examination was unremarkable. The white blood cells count was 10.3 cells/cm^3 (neutrophil predominance) and hemoglobin was 10.8 mg/dL. Routine chemistries were normal. A 4-mm punch biopsy taken from the right forearm revealed foamy macrophages in the dermis with an intense neutrophilic infiltrate extending into the subcutaneous fat (Figure 2A). A lower magnification view (x4) showed intense inflammatory cell infiltrate that outlined the dermal vasculature and extended into the subcutaneous fat. There was a perivascular mixed inflammatory infiltrate and fibrinoid necrosis of small vessels. Fite stain showed beaded and granular acid-fast bacilli within the histiocytes and focally within cutaneous

nerve twigs (Figure 2B). Polymerase chain reaction for *M leprae* DNA was positive. Tissue culture was negative for bacteria and fungi. The biopsy was reviewed by the US National Hansen's Disease Program in Carville, Louisiana. Compared with a biopsy from 2015, the inflammatory infiltrates were diminished and the bacilli had a degenerating appearance. These findings were consistent with appropriate response to antimycobacterial therapy. Treatment with thalidomide 100 mg daily was initiated with improvement in the appearance of the skin lesions (Figure 3). A repeat biopsy performed 6 months later showed lack of neutrophilic infiltrates and decreased number of acid-fast bacilli. Monthly skin scrapings from affected sites showed progressively decreased bacterial load.

Discussion

The distinction between persistent infection (disease progression while on treatment or relapse posttreatment) and immunologic reactions in leprosy can be challenging. Persistent infection is less common and often reflects poor adherence or incomplete treatment. Antimycobacterial drug resistance can also occur, but it is rare. In persistent infection, skin biopsy typically shows a rising bacterial load. The presence of bacilli, however, does not always equate to active disease. In heavily infected lepromatous leprosy patients, dead bacilli can remain in the tissues and nerves for up to 10 years.² These individuals have macrophage dysfunction, which contributes to a slow clearance of mycobacteria. Viability testing can play a role in the evaluation of patients with persistent bacilli. The method frequently used is the mouse footpad technique. This method is time consuming, expensive, labor-intensive, and lacks sensitivity and specificity of comparable bacterial cultures. However, there is no accepted alternative for cultivating *M leprae/leprosum*.³ Another method to assess treatment response is the comparison of skin biopsies performed at regular (1-2 year) intervals and evaluating reduction of inflammation and decline of bacilli in the tissues. In our patient, persistent infection was unlikely due to the decrease and degeneration of mycobacteria observed on skin biopsy after prolonged treatment.

There are 2 types of immunological reactions in leprosy: Type 1 reaction (T1R)/reversal reaction and T2R/erythema nodosum leprosum. T1R typically occurs in patients with borderline disease, while T2R occurs in patients with lepromatous disease. These reactions can be seen in up to 50% of patients¹ and there is no temporal correlation to treatment.⁴ In our patient, T2R was diagnosed based on a compatible clinical presentation and the presence of leukocytoclastic vasculitis and panniculitis with neutrophilia in skin biopsy. The characteristic biopsy findings in T2R are infiltration of neutrophils superimposed on chronic inflammation and detection of *M leprae* by staining or polymerase chain reaction methods. Neutrophils are rare in all other types of leprosy lesions. In addition,

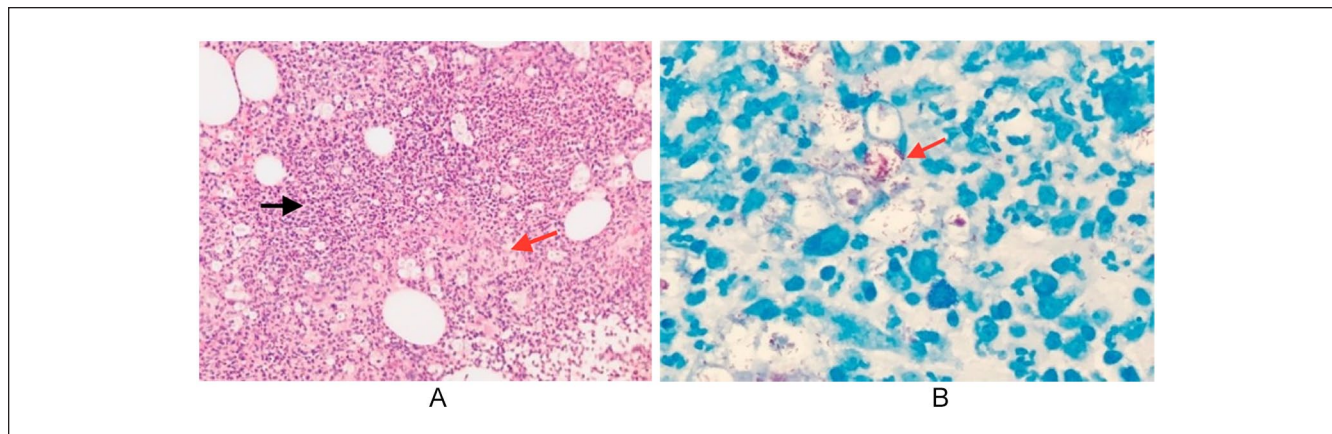


Figure 2. (A) Hematoxylin and eosin stain of punch biopsy of forearms. Foamy macrophages (red arrow) in the dermis with an intense neutrophilic infiltrate (black arrow) forming abscesses (40 \times). (B) Fite stain of punch biopsy of the forearms. It shows acid-fast organisms (1000 \times) with beaded, granular and degenerated appearance within histiocytes (red arrow). Tissue polymerase chain reaction (PCR) was positive for *Mycobacterium leprae* DNA. A positive PCR result does not mean viable bacteria are present.



Figure 3. Image of the anterior forearms post-treatment. Decreased nodularity and hyperpigmentation of the skin after 6 months of treatment with thalidomide.

patients with immunologic reactions typically respond to systemic corticosteroid and other forms of immunosuppression, unlike those with persistent infection.⁵

Conclusion

Due to migration and globalization, leprosy will continue to be reported in the United States. In 2015 alone, 178 new cases were reported.⁶ Clinicians should be aware of the potential complications associated with this infection including persistent infection and immunologic reactions. A high index of suspicion and accurate interpretation of skin biopsy results are essential. The US National Hansen's Disease Program provides consultation services and assists clinicians in the diagnosis, treatment, and monitoring of challenging cases.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

Informed Consent

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