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A Challenging Case of Domestically Acquired Leprosy in the Southern United States

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Hansen's disease (HD) is rare in the United States, but a steady number of cases are diagnosed annually, especially in southern areas where armadillos are present. Challenges associated with erythema nodosum leprosum (ENL), a complication of multibacillary leprosy, call for novel regimens. We present a case of a man with recalcitrant ENL from HD likely acquired in the United States. He required a combination of 4 drugs to control chronic ENL.

Keywords. Hansen's disease; leprosy; Type 2 reaction; erythema nodosum leprosum.

Hansen's disease (HD), or leprosy, is an infectious disease caused by *Mycobacterium leprae*. Affecting the nerves, skin, eyes, and nasal mucosa, it has the potential to lead to severe disability and nerve damage if treatment is delayed [1, 2]. In the United States, 178 new cases were reported in 2015 [3]. Interestingly, there has been an increase in HD in the south, predominantly in Florida, since 2016 [4–9]. This disease is treatable by combination antibiotic therapy; however, significant challenges remain. Type 1 and Type 2 leprosy reactions may cause severe immune-mediated episodes [1, 10]. This case will focus on treatment for Type 2 reactions (erythema nodosum leprosum [ENL]), a systemic immune complex–mediated syndrome, which can be recalcitrant and resistant to treatment.

CASE

A 43-year-old, previously healthy male presented with a 1-year history of erythematous lesions on his legs, which then spread to his trunk and other extremities. He was born in the United States, spent some time in Germany as a child, and traveled once to the Bahamas as a young adult. He grew up in Florida and has been in Georgia for the last 19 years. The patient knew of a family friend with HD but was never in contact with her. He is a carpenter by trade and often works outdoors.

On presentation, the patient reported feelings of occasional parasthesias in the right calf. On exam, he had scattered, hyperpigmented, maculopapular lesions on the extremities and back (Figure 1). The left ankle had decreased sensation over a hypopigmented skin lesion, but intact sensation was noted over the hands and feet. The skin biopsy showed perineural infiltrates, and numerous acid-fast bacilli in macrophages were noted on Fite consistent with lepromatous leprosy. He was started on multidrug therapy (MDT), which included clofazimine, rifampin, and dapsone. He was also given a 1-month prednisone taper for swollen ankles and concern for possible Type 1 reaction.

Although his nerve symptoms and skin lesions improved on MDT, 2 months later the patient presented with diffuse tender skin nodules (Figure 2), swollen joints, and fever, consistent with Type 2 reaction, or ENL. He was initially treated with prednisone at 40 mg daily (Table 1), later tapered to 20 mg daily, but required repeated bursts of 30–40 mg daily. The patient was hesitant to try thalidomide due to the side effects. After a discussion on potential options, methotrexate was added to prednisone, and ultimately its dose was increased to 20 mg per week. There was initial improvement, but he then had recurrent ENL flares (painful nodules, fever, joint pain and swelling) on this regimen (Table 1). At that point, thalidomide at 100 mg/d was prescribed and methotrexate discontinued, as it did not seem to have had a significant or sustained effect on symptoms. Prednisone was continued and initially was weaned to 15 mg/d with the addition of thalidomide. However, fatigue limited the titration of thalidomide >100 mg/d, and with periodic ENL flares, a dosage of prednisone 15 mg daily was unsustainable; he was never able to wean down under 20 mg of prednisone/d for >3 months at a time. Most recently, 4 years after diagnosis of ENL, methotrexate at 10 mg/wk was added to thalidomide at 50 mg/d and 100 mg/d of clofazimine (for anti-inflammatory properties), as well as decreasing doses of prednisone. He has made progress and has had fewer ENL flares.

DISCUSSION

Clinically, the Ridley-Jopling classification uses immune responses to the infection and histopathology to classify HD into categories spanning tuberculoid to lepromatous [11]. Patients with borderline and lepromatous disease are at risk of erythema nodosum leprosum, with up to 50% suffering from this complication. ENL is characterized by painful skin nodules,

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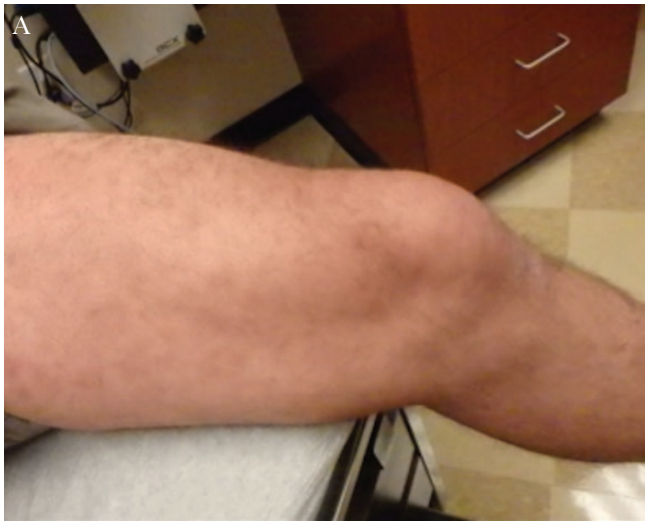


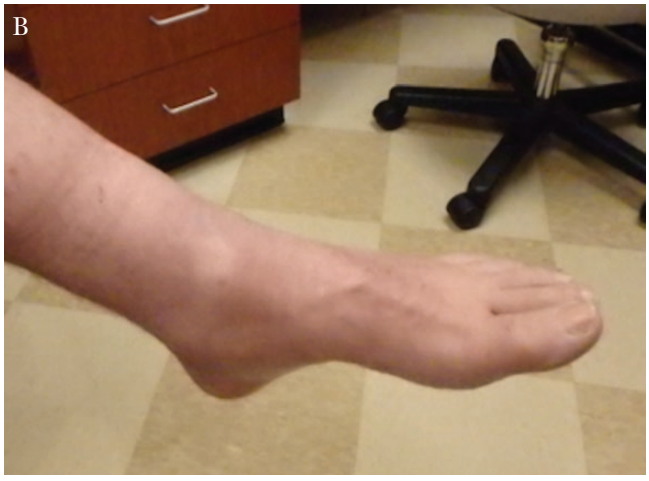
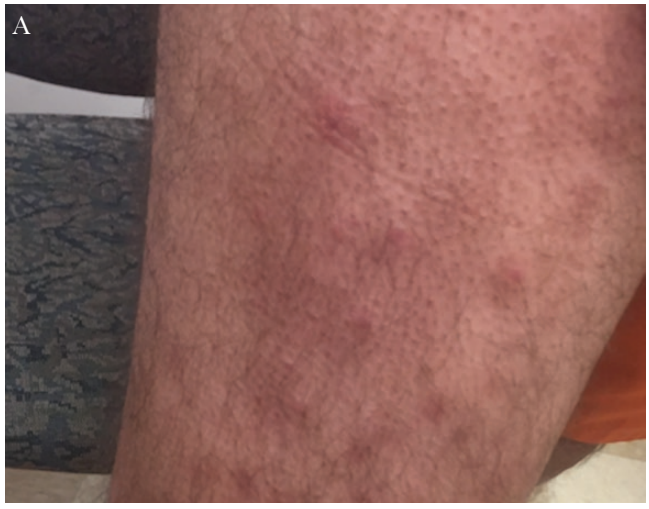


Figure 1. Photographs of case patient at the time of diagnosis. Subtle hyperpigmented papules are noted on the upper leg, with a large hypopigmented, anesthetic lesion proximal to the left medial malleolus. Photos shared with permission from the patient.



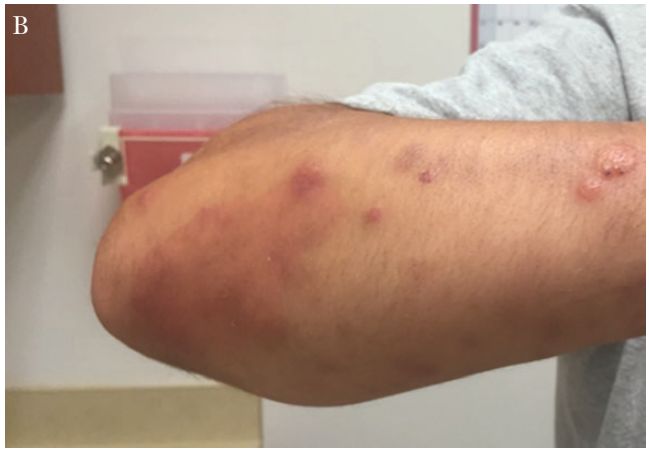


Figure 2. Photographs of case patient with erythema nodosum leprosum nodular lesions on the leg (A) and forearm (B).

systemic symptoms like fever, and sometimes neuritis [1, 10]. Thalidomide is generally considered the treatment of choice for ENL, but limited availability, teratogenicity, and side effects often limit its use [12]. Corticosteroids, therefore, are frequently prescribed instead, but often require very high doses and prolonged therapy, increasing the risk of potentially serious adverse effects. Patients who transition from prednisone to thalidomide are often able to wean completely off prednisone and continue to control ENL with thalidomide alone [12]. However, in our patient, this was not the case, with attempts at steroid-sparing regimens (first methotrexate and then thalidomide) thwarted by recalcitrant symptoms and side effects.

Dedicated studies investigating multidrug therapy for ENL are lacking; however, some 2-drug combinations have been used and were initially attempted in the presented case. A study comparing thalidomide and prednisone with clofazimine and prednisone in patients with chronic ENL showed that thalidomide with prednisone was more efficient in treating recurrent Type 2 reactions [13]. Due to the long-term adverse effects of steroids, though, it is paramount to taper prednisone to lower levels, scaling up for new ENL flares as needed. However, this has been a challenge, as our patient was unable to control flares on <20 mg per day of prednisone, with the sedating effects of thalidomide limiting use at higher doses.

Methotrexate, whose effectiveness in treatment-resistant ENL is still being studied, also has anti-inflammatory properties and is thought to suppress immune responses [14, 15]. A recent study followed the disease progression of 9 severe ENL patients who were unresponsive to clofazimine and prednisolone treatment. With a combination of methotrexate and prednisone treatment for 30–36 months, the patients showed a gradual but steady improvement that led to sustained remission of ENL long after the study's conclusion [15]. Our patient, though, did not respond to 20 mg weekly of methotrexate combined with prednisone. It is important to note that thalidomide was not a

Table 1. Timeline of Patient Symptoms and Treatment Regimens

Timeline	Symptoms	Treatment Notes
T: 1 year before presentation	Erythematous lesions develop and spread	—
Time 0 (1st visit to HD clinic)	Parasthesias, bilateral ankle swelling, maculopapular lesions on extremities and back	1. MDT started: clofazimine, rifampin, dapsone 2. 40 mg of prednisone for concern of Type 1 reaction (swollen joints), tapering down and off within 4 wk
2 mo	Type 2 reaction: tender skin nodules, fever, swollen joints	Restarted prednisone at 40 mg with quick taper to 20 mg daily
3 mo	Continued ENL symptoms	Brief attempt at 10 mg prednisone daily, but then brought up to 20 mg daily; clofazimine increased to 200 mg daily
6 mo	Symptoms initially controlled on above, then new flare with nodules and fever	Methotrexate started—titrated up to 20 mg/wk Prednisone (20 mg/d)
7–10 mo	Improved symptoms	Prednisone weaned to 15 mg daily
11 mo	ENL symptoms worsen, with more frequent flares of nodules, fevers, joint swelling	Methotrexate 20 mg/wk Prednisone 40 mg intermittently
12 mo	Prednisone wean attempted	Thalidomide started 100 mg/d then stopped Clofazimine decreased to 50 mg/d due to risk of crystal enteropathy
12 –18 mo	Unable to control flares with 20 mg of prednisone	Thalidomide 100 mg daily Prednisone 25–30 mg daily
18–42 mo	Fewer flares	Thalidomide 100 mg daily Prednisone 15–20 mg daily MDT stopped at 24 mo
42 mo	Patient wishes to wean off thalidomide	Thalidomide 50 mg daily Prednisone 15 mg daily
42–48 mo	ENL flares increase with weaning of thalidomide	Clofazimine restarted—200 mg/d Thalidomide 50 mg daily Prednisone 20–30 mg daily
Currently (4 y after diagnosis)	Progress with fewer ENL flares	Methotrexate (10 mg/wk) Thalidomide (50 mg/d) Clofazimine (100 mg/d) Prednisone 10–15 mg/d

Abbreviations: ENL, erythema nodosum leprosum; HD, Hansen's disease; MDT, multidrug therapy.

part of these early treatment regimens. However, with combination therapy, there has been significant improvement with 4 drugs: prednisone, thalidomide, methotrexate, and clofazimine, all at low doses. This would support the use of multiple drugs to both better control symptoms and reduce risk of serious adverse events, but more formal studies need to be done to compare regimens. Use of other treatments, such as azathioprine, infliximab, and etanercept, has been reported and may be important in situations where thalidomide is either restricted or not well regulated [16–19].

The patient's epidemiological risk factors were also an interesting part of this case. He denied any foreign residence or significant international travel; therefore, he likely acquired HD through the armadillo reservoir. He reports having no direct contact with armadillos except seeing them on his property. Though there are still many unknown factors about transmission of this disease, the most accepted route is person-to-person through nasal droplets. Armadillos that are naturally infected with the bacteria have also been proven reservoirs, with potential transmission through soil or free-living ameoba [9, 20, 21]. Cases that are considered to be domestic are most common in Florida and from Texas to Georgia [9, 21].

The patient living on armadillo-inhabited land indicates a greater possibility of indirect exposure to *M. leprae* [9]. As carpentry is a profession that requires frequent exposure to house dust and soil, the question of whether these vocations pose an increased risk for Hansen's disease in areas with rising incidence presents an interesting topic of further study.

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Consent. The patient described in this case has given full, signed, informed consent to describe his medical treatment and to use deidentified photographs of his skin.

Author contributions. S.M. and J.K.F. contributed equally to the writing and editing of the manuscript.

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