Leprosy mimicking basal cell carcinoma in a patient on fingolimod

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Key words: basal cell carcinoma; cancer; fingolimod; lepromatous leprosy; leprosy; *Mycobacterium*.

INTRODUCTION

Leprosy, also known as Hansen disease, is a chronic bacterial disease caused by *Mycobacterium leprae*. *M. leprae* has low pathogenicity and virulence, developing over many months to even decades, and has the potential to cause extensive damage to the skin and peripheral nervous system.[1] Here we present a patient with a history of multiple sclerosis (MS) who presented with 3 lesions that clinically appeared like basal cell carcinomas (BCC). After biopsies were collected, pathology revealed lepromatous leprosy (LL).

METHODS

We conducted a PubMed search using various combinations of the following key words and phrases: "fingolimod," "leprosy," "multiple sclerosis," and "basal cell carcinoma."

CASE REPORT

A 52-year-old woman with a past medical history of MS, diagnosed in 2007 by magnetic resonance imaging, presented to her dermatologist with a 1-year history of erythematous papules on her cheeks. Previous MS treatment included interferon injections, glatiramer acetate, immunoglobulin infusions, mitoxantrone, and natalizumab. Upon presentation, the patient was on fingolimod (FTY720, Gilenya; Novartis Pharma Stein AG, Stein, Switzerland), and had been for 5 years.

On exam, erythematous, pearly papules were noted on her right medial cheek, right lateral cheek, and left lower cheek (Fig 1). The patient's eyebrows and eyelashes were preserved, and no other concerning lesions were noted on her trunk or extremities. Three punch biopsies, 1 of each lesion, were performed.

Abbreviations used:

BCC:	basal cell carcinoma
ENL:	erythema nodosum leprosum
LL:	lepromatous leprosy
MS:	multiple sclerosis

Microscopic examination revealed chronic inflammatory infiltrates involving >90% of the dermis biopsy. The infiltrates consisted of foamy histiocytes and disordered aggregates of lymphocytes. Fite stain revealed numerous acid-fast bacilli within the histiocytes and cutaneous nerves (Fig 2). Polymerase chain reaction analysis was positive for *M. leprae* DNA.

The patient was referred to the National Hansen's Disease Program for evaluation. The program conducted an upper extremity peripheral nerve exam, which revealed sensory loss of the right radial and median nerves, along with muscle weakness in the left radial nerve and bilateral ulnar and median nerves. Tenderness was noted bilaterally at the radial sensory nerve. An examination of the lower extremity revealed areas of loss of protective sensation in both feet. The patient's left lower extremity was slightly weaker than her right, but no nerve enlargement or tenderness was noted in her lower extremities.

The patient initiated triple therapy with rifampin 600 mg daily, clarithromycin 500 mg daily, and minocycline 100 mg daily. Because the patient had lymphopenia caused by fingolimod, she was not treated with dapsone. In addition, the patient

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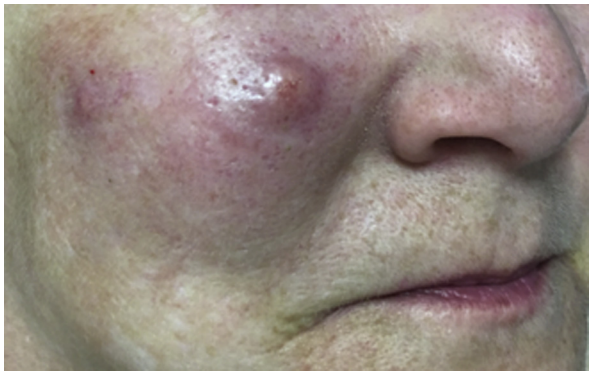

Fig 1. Right cheek lesions at initial visit.

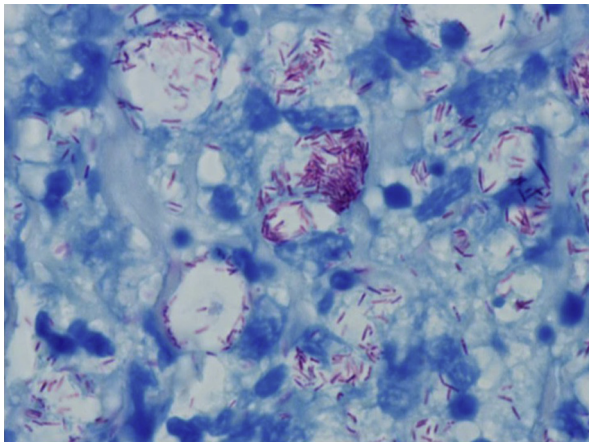

Fig 2. Acid-fast bacilli within histiocytes and cutaneous nerves. (Fite stain; original magnification: ×1000.)

deferred treatment with clofazimine because its use increases the risk for unsightly skin discoloration within the lesions, which were present on her face.

Two weeks after starting triple therapy, the patient's facial lesions worsened, becoming more erythematous (Fig 3). This treatment failure confirmed erythema nodosum leprosum (ENL). Multiple foci with acute infiltrates of polymorphs were present on her initial biopsy, which is indicative of ENL (Fig 4).

To avoid worsening MS symptoms, thalidomide was not used to treat the ENL. Instead, rifampin was decreased to monthly doses, and the patient began weekly doses of methotrexate 10 mg and daily doses of prednisone 10 mg. Her facial lesions continued to worsen, and the patient was unable to tolerate the 10 mg/day prednisone dosage because of its mood change side effects. At that time, methotrexate was increased to 20 mg weekly, prednisone was decreased to 5 mg daily, the patient consented to clofazimine use at a high dose of 200 mg daily because of its anti-inflammatory properties, and minocycline was discontinued.

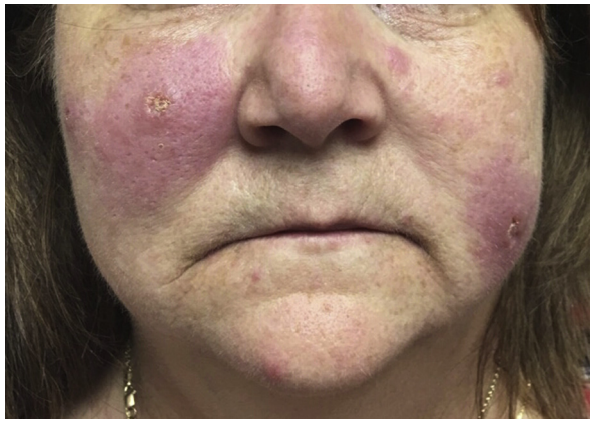

Fig 3. Facial lesions 2 weeks after triple therapy was initiated.

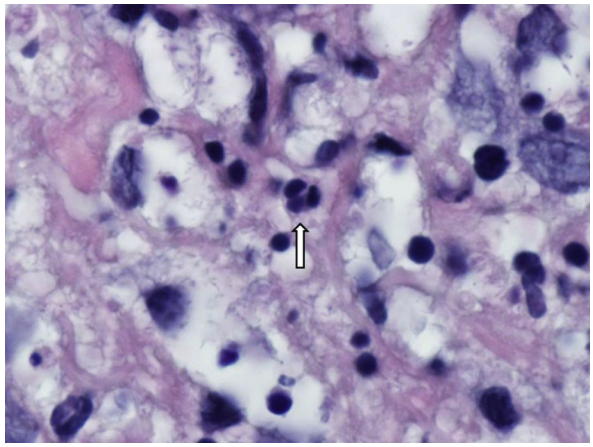

Fig 4. Multiple foci with acute infiltrates of polymorphs (*arrow*). (Hematoxylin-eosin stain; original magnification: ×1000.)

DISCUSSION

Leprosy, also known as Hansen disease, is a chronic bacterial disease caused by *M. leprae*. In 2014, approximately 175 new cases of leprosy were reported in the United States.[2] Of these cases, 73% were discovered in Arkansas, California, Florida, Hawaii, Louisiana, New York, and Texas.[2] *M. leprae* is difficult to diagnosis because of its slow replication and long incubation time. The average incubation period is 4-10 years but can range from <1 year to >30 years.[1]

Leprosy has a wide range of clinical features, differing between the 6 types: LL, borderline LL, midborderline leprosy, tuberculoid leprosy, borderline tuberculoid leprosy, and indeterminate leprosy. The LL type most commonly arises in patients with depressed cell-mediated immunity and contains the largest number of bacilli within lesions, while the tuberculoid type more commonly occurs in patients with intact cell-mediated immunity and has the least

amount of bacilli in tissues.[1] The lesions vary in appearance, ranging from hypopigmented to erythematous macules, papules, nodules, and plaques. Dermatologic conditions such as pityriasis versicolor, sarcoidosis, psoriasis, syphilis, and lymphoma can present similarly, leading to a risk of misdiagnosis.[1]

The patient described was immunosuppressed due to the fingolimod therapy. Fingolimod is a sphingosine-1-phoshate partial agonist, which in turn down regulates sphingosine-1-phoshate receptors on cells, resulting in the sequestration of lymphocytes in lymph nodes.[3,4] Drug-induced lymphopenia is a known adverse side effect and is closely monitored for while taking fingolimod.[3,4]

BCC develops in the skin secondary to ultraviolet radiation damage, leading to depressed cell-mediated immunity. In February 2016, the Food and Drug Administration issued a warning that fingolimod is associated with BCC.[5] In 2-year, placebo-controlled trials the incidence of BCC was 2% in those on the drug compared with 1% in those on the placebo.[5] The cell-mediated immunosuppression induced by fingolimod could be related to the increased risk for BCC. BCC classically presents as a pearly papule or nodule with elevated, rolled borders and telangiectasias. The above illustrated case of LL presented with clinical characteristics similar to a BCC.

Leprosy patients can develop severe complications, such as a reversal reaction or ENL. These inflammatory response complications might present before, during, or after treatment of leprosy.[6] ENL is categorized as a T_H2 response involving polymorphic neutrophilic infiltrates in the affected lesions, representing an acute wide-spread inflammatory response.[6-8] ENL is more common than a reversal reaction, with occurrence rates as high as 50%-64%.[6,9] ENL is often treated with steroids, high doses of clofazimine, or thalidomide.[10]

To our knowledge, this is the first published case of a patient being diagnosed with leprosy while on fingolimod and the first published case of leprosy mimicking BCC. Leprosy can be a challenging diagnosis for physicians because the disease has multiple subtypes with a variety of clinical presentations. Because of the severity of the disease and potential disfiguring complications, it is of utmost importance that leprosy not be misdiagnosed. Physicians with patients on biologics should have a high suspicion for an underlying medical condition when these patients develop new skin lesions or systemic symptoms.

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