Development of Leprosy and Type 1 Leprosy Reactions after Treatment with Infliximab: A Report of 2 Cases

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Humanized monoclonal antibodies to tumor necrosis factor–α are valuable for the treatment of rheumatologic conditions, but they have been associated with the development of serious infections. We report the first 2 cases of leprosy developing after treatment with infliximab. After discontinuation of infliximab, both patients developed type 1 (“reversal”) leprosy reactions.

Humanized monoclonal antibodies that bind TNF-α, such as infliximab and etanercept, have rapidly become widely used in the management of severe rheumatologic conditions [1]. However, use of these agents has also been associated with the development or reactivation of infections controlled by cell-mediated immunity [2–5]. Leprosy, or Hansen disease (HD), is uncommon in the United States, and when it occurs, it typically develops very slowly. We observed 2 patients in the United States who received infliximab for arthritis and subsequently developed borderline lepromatous HD in a relatively short time. In addition, recovery from this infection was accompanied in both patients by the development of “reversal,” or type 1, reactions (T1R). These reactions are characterized clinically by malaise and exacerbation of the preexisting lesions, with erythema and tenderness, often accompanied by neuritis and severe edema of the hands or feet [6].

Case reports. Patient 1 was a 60-year-old white male from Louisiana who had diffuse polyarthritis for 5 years prior to hospital admission, which was treated with corticosteroids and courses of methotrexate (for 5 years) and hydroxychloroquine (for 4 years). An abdominal rash, thought to be caused by an allergy to ibuprofen, developed 4 years prior to admission and resolved after discontinuation of the drug. He received 3 courses of infliximab; the last was given 3 months prior to hospital admission. One month after the patient received the first dose of infliximab, he developed a rash on 1 extremity that progressed to all extremities. The results of a biopsy of this lesion were interpreted as indicating lymphohistiocytic granulomatous dermatitis. Results of a later skin biopsy suggested HD, and he was referred to the National Hansen’s Disease Program for evaluation.

The patient had no family history of HD, had never traveled outside of the United States, and had no significant history of contact with armadillos. He had type 1 diabetes mellitus, hypertension, and cardiovascular disease. A large, flat plaque was noted on the left lower extremity, and there were numerous smaller plaques on all extremities, except for the patient’s face and trunk. He had diffuse swelling of both hands and feet and induration and erythema of the dorsum of both hands. Marked onchomycosis was noted on both feet. The right peroneal nerve was slightly tender on palpation but was not enlarged. Sensory testing with Semmes-Weinstein monofilaments [7] revealed focal loss of protective sensation on the plantar surfaces of both feet, with normal sensation in the hands. Swelling, erythema, and warmth were noted on the left olecranon bursa.

The patient’s leukocyte count was 9500 cells/mm³, his erythrocyte sedimentation rate was 42 mL/dL, and his hemoglobin level was 13.4 g/dL. The results of rheumatoid factor and antinuclear antibody tests were negative.

A biopsy of a lesion on the patient’s right forearm revealed characteristic features of borderline lepromatous HD with moderate numbers of bacilli [8] (figure 1A). Examination of the tissue by PCR identified the characteristic 360–base pair fragment of the gene for the Mycobacterium leprae 18-kD protein [9].

The patient was treated with the National Hansen’s Disease Program multidrug therapy (MDT) of dapsone (100 mg daily), clofazimine (50 mg daily), and rifampicin (300 mg monthly) [10]. Minocycline (100 mg daily) was substituted for dapsone after the patient developed severe dapsone-induced anemia. He continued to receive methotrexate and corticosteroids for arthritis, but infliximab was discontinued.

One month after starting MDT, the patient developed a marked increase of erythema and induration of the skin lesions, characteristic of a T1R. A biopsy revealed slightly greater organization of the inflammatory infiltrate, increased lymphocytic clustering, and more multinucleated giant cells—findings consistent with a T1R (figure 1B). He continued therapy with methotrexate, and the prednisone dosage was increased from

Received 27 January 2006; accepted 22 March 2006; electronically published 9 June 2006.
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Clinical Infectious Diseases 2006;43:e19–22
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1058-4838/2006/4302-00E2
Figure 1. Histopathological progression of cutaneous lesions in patient 1. A. The initial skin biopsy revealed features of borderline lepromatous leprosy, with a disorganized inflammatory infiltrate in which vacuolated macrophages predominated. Occasional multinucleated giant cells were also noted (hematoxylin-eosin staining; original magnification, ×250). Fite’s staining revealed numerous acid-fast bacilli (inset; original magnification, ×1000). B. A biopsy 1 month later revealed greater organization of the inflammatory infiltrate and increased lymphocytic clustering, with more multinucleated giant cells, consistent with a type 1 leprosy reaction (hematoxylin-eosin staining; original magnification, ×250). C. A third biopsy performed during another reaction 3 years after diagnosis revealed an increasingly organized granulomatous process (hematoxylin-eosin staining; original magnification, ×250). The bar is equal to 100 microns.

10 mg to 20 mg daily; after 4 months, this was tapered to 10 mg daily, and there was both clinical and histological evidence of resolution of the reaction. During the third year of treatment, after prednisone had been discontinued and methotrexate had been reduced, the patient experienced another T1R (figure 1C). This reaction also responded to corticosteroid treatment. After 4 years, the cutaneous lesions had resolved, and MDT was discontinued. Results of a skin biopsy performed 5 years after diagnosis confirmed advanced regression of the lesion with no residual bacilli.

Patient 2 was a 76-year-old white female from Texas who had a long history of rheumatoid arthritis with bony deformities, severe secondary shoulder degeneration, and osteoporosis. She had been treated with prednisone at varying doses for 10 years and with hydroxychloroquine plus methotrexate and leflunomide plus methotrexate. She first received infliximab therapy 18 months prior to hospital admission and had the last course 3 months prior to admission. Infliximab was given irregularly because of repeated development of a skin rash that resolved when the drug was discontinued. Results of a skin biopsy suggested a diagnosis of HD, and she was referred to the National Hansen’s Disease Program for evaluation.

At hospital admission, the patient was receiving prednisone (20 mg daily) but had received no infliximab for 2 weeks. She had no prior history of HD. Her husband, who had died the previous year, had had considerable exposure to armadillos (he hunted them), and he reportedly had had an extensive skin rash and numbness of his hands and feet but had refused to seek medical attention.

At admission, the patient’s temperature was 38.2°C. Multiple raised, pink, warm nodules and plaques were observed on all extremities, chest, and back, as well as bilaterally on the face. Sensory testing with Semmes-Weinstein monofilaments revealed the loss of protective sensation in both feet, but sensory capacity was normal in both hands. She had characteristic features of rheumatoid arthritis.

Results of a skin biopsy revealed histopathological features of borderline lepromatous HD [8]. Examination of the tissue by PCR identified the *M. leprae* 18-kD protein gene [10].

Nerve conduction studies revealed neuropathic changes in all extremities, with abnormal compound muscle action potentials and sensory nerve action potentials. The patient’s WBC count was 7400 cells/ mm³, her hemoglobin level was 11.6 g/dL, her erythrocyte sedimentation rate was 198 mL/dL, her rheumatoid factor titer was 1:8, and her antinuclear antibody titer was 1:80 in a smooth pattern.

The patient was treated with standard MDT as described above, and she continued to receive prednisone (5 mg daily), but infliximab was discontinued. One month after starting MDT, she developed clinical signs of a T1R, and her leukocyte count was 12,900 cells/ mm³ (76.9% granulocytes, 19.7% lym-
phocytes). The prednisone dosage was increased to 30 mg and then to 40 mg daily to control the reaction, and after 1 month, the dosage was tapered slowly.

A biopsy after 6 months of MDT revealed increased organization and decreased extent of inflammation, as well as a reduced bacterial load, consistent with upgrading of the immune response. Approximately 1 year later, the patient died because of an unrelated illness.

Discussion. Three aspects of these 2 cases are particularly notable. First, the development of HD after receipt of infliximab in 2 native-born individuals in the United States is remarkable, because only 130–150 new patients receive a diagnosis of HD in the United States annually, and <15 of these are native-born residents of Louisiana and Texas [11]. No meaningful statistical analysis can be performed with these small numbers, but this occurrence is remarkable. The diagnosis of HD in both patients was firmly established by clinical and histopathological criteria and by molecular identification of M. leprae DNA in the biopsy specimens.

Second, M. leprae infection progressed more rapidly in both of these patients than is typical for this slow-growing pathogen. They developed the borderline lepromatous form of the disease (i.e., a large bacterial load) within 1–2 years after receiving infliximab, which is shorter than the typical incubation time of 3–5 years for this form of HD. Both patients probably had pre-existing, subclinical HD, which is analogous to the activation of latent tuberculosis after infliximab treatment [2]. Both patients were apparently able to maintain sufficient immunity to M. leprae to contain the infection, even through years of other immunosuppressive treatments, highlighting the unique abrogation of cellular immunity induced by functional depletion of TNF-α by infliximab. Experimental studies in mice made transiently deficient in TNF-α function have also demonstrated the dramatic insufficiency of cellular immunity that results from such treatment [12]. This may not be equally true of all TNF inhibitors, however, because other anti-TNF agents are reported to have lower risks of infection, possibly due to differences in their binding of soluble and membrane-bound TNF-α [13].

Third, after discontinuation of infliximab and initiation of antimicrobial treatment for leprosy, both patients developed a T1R, which usually affects only ∼40% of borderline lepromatous leprosy patients [14]. The reactions in our patients may have been the result of rapid restoration of preexisting immunity that had been transiently impaired by infliximab treatment, which is similar to the T1Rs that occur as an immune reconstitution phenomenon in persons with HD and AIDS after receiving HAART [15–17]. However, leprosy is not associated with the loss of CD4+ cells or the broad immunodeficiency observed in persons with untreated HIV infection or AIDS, which suggests that anti-TNF therapy has a particular effect that is not dependant on T cell immunodeficiency.

In both of our patients, M. leprae infection responded satisfactorily to standard antimicrobial treatment, although resolution was slow, especially in the first patient. The continued requirement for corticosteroid and immunosuppressive treatment for rheumatoid arthritis is likely to have retarded both the bactericidal activity of the antimicrobials and the local immune response of the patients. As a result of the experience with these 2 patients, we caution that, among persons with overt or latent M. leprae infection, inhibition of TNF-α by infliximab may increase the risk of (1) the development of clinical disease, (2) accelerated progression of the infection, and (3) subsequent immunologic complications of leprosy on withdrawal of the anti-TNF-α treatment.

Acknowledgments

Financial support. American Leprosy Missions (to D.M.S. and T.P.G.).

Potential conflicts of interest. All authors: no conflicts.

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