Methotrexate Treatment for Type 1 (Reversal) Leprosy Reactions

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Corticosteroids are the drugs of choice for treatment of type 1 leprosy reactions, but when these agents cannot be used because of their adverse effects, alternative treatments are needed. We report the first case, to our knowledge, of a type 1 leprosy reaction that was successfully treated with methotrexate in a patient intolerant to corticosteroids who had borderline lepromatous leprosy.

Leprosy is a chronic infectious disease caused by Mycobacterium leprae that primarily affects the skin and the peripheral nerves. In the past few years, the global prevalence has been ~460,000 cases, but there has been an overall decrease in the prevalence that has resulted from the introduction of multiple-drug therapy. Most cases occur in the developing world; 83% of registered cases have been concentrated in only 6 countries: India, Brazil, Burma, Indonesia, Madagascar, and Nepal [1]. The large number of people who are migrating from countries where leprosy is endemic to countries where it is not may lead to more cases in the latter countries, where physicians may not suspect persons to present with leprosy. The majority of new immigrants with leprosy develop symptoms within 1 year after migration [2].

Type 1 leprosy reactions (i.e., reversal reactions) indicate a change in cell-mediated immunity and occur in patients with borderline forms of leprosy. The clinical manifestations of these reactions are edema and erythema of skin lesions, as well as neuritis. The treatment of choice is corticosteroid therapy (prednisolone, 40–60 mg per day, with the dose decreasing by 5 mg every 2–4 weeks after evidence of improvement). In type 2 leprosy reactions (i.e., erythema nodosum leprosum), which are seen in patients with borderline-lepromatous and lepromatous leprosy, a systemic inflammatory response to the deposition of extravascular immune complexes occurs. Thalidomide (400 mg daily) is the drug of choice for treatment, although corticosteroids and clofazimine can also be administered [3].

Case report. We report an extraordinary case of a 58-year-old man from the Dominican Republic who had been living in Spain since 1998. In 1998, he received propranolol treatment (20 mg every 12 h) for mild hypertension and levothyroxine treatment (50 mg per day) for hypothyroidism. In January 2002, the patient presented with asymptomatic maculae on his left ankle that had been misdiagnosed as sarcoidosis by a dermatologist after examination of a biopsy specimen from the lesion. He was treated with topical corticosteroids and experienced clinical improvement. One year later, the patient was again referred to the hospital, because the same lesions had reappeared, new lesions had appeared all over his body, and both ulnar nerves were enlarged. Sensory testing with monofilaments was performed at that time, but tests revealed no damage in the median, tibial, and peroneal nerves. Skin slits were obtained from the lesions, as were biopsy specimens. Alcoholic acid-fast bacilli were seen in both the biopsy specimen and the skin smears, and a final diagnosis of borderline lepromatous leprosy was made. Skin slits revealed a bacteriological index of 5+ and a morphological index of 15%. Therapy with rifampin (600 mg per month), dapsone (100 mg per day), and clofazimine (300 mg per month plus 50 mg per day) was started, as recommended by the World Health Organization for treatment of multibacillary leprosy.

Twenty days after the commencement of treatment, the patient presented with fever, erythema, and severe edema of the skin lesions, as well as neuritis in both ulnar nerves (figure 1). The lesions were swollen, very erythematous, and tender, and type 1 leprosy reaction was diagnosed. The dosage of clofazimine was increased to 300 mg per day, and salicylic acid (1 g every 6 h) was added to the treatment regimen. Two days later, corticosteroid treatment (60 mg per day) was started, with a progressive decrease in the dosage of 5 mg every 2 weeks. Two months later, the lesions had improved, with reduced ulnar nerve pain. However, the patient was experiencing severe anxiety, polyphagia, depression, and severe hyperglycemia; this necessitated hospital admission, because the patient’s hyperosmolar state required treatment with fluids and insulin. Because of these adverse effects, the corticosteroid dosage was decreased to 20 mg per day, with progressive reduction in the dosage...
Figure 1. Patient with severe type 1 leprosy reaction after receipt of multidrug therapy (rifampicin, 600 mg per month; dapsone, 100 mg per day; and clofazimine, 300 mg per month plus 50 mg per day).

continuing as before. After 1 month, skin lesions and paresthesia worsened in both feet and arms; therefore, the dosage of corticosteroids had to be increased again from 5 mg per day to 20 mg per day. Five months later, the patient was again admitted to the hospital, with dyspnea, edema of the feet, and worsening of hypertension. Electrocardiography and echocardiography revealed dilatated cardiomyopathy that was probably associated with steroid treatment and that required treatment with angiotensin converter enzyme inhibitors and diuretics.

The patient had insulin-dependent diabetes, hypertension, heart failure with dilatated cardiomyopathy, psychological changes (depression and polyphagia), centripetal obesity, and facial plethora that were suggestive of Cushing syndrome resulting from the administration of steroids. At this point, management of the reaction was very difficult, because if the steroid dosage was decreased, the type 1 leprosy reaction worsened. Nevertheless, adverse effects were too significant to maintain this treatment. We decided to start administering methotrexate, a drug that has been used for many years to treat lupus and psoriasis but that has, to our knowledge, never been used before to treat type 1 leprosy reactions. The dose of corticosteroids was reduced gradually. Methotrexate was initially administered in weekly 5-mg doses and was given with folic acid, with periodic blood cell counts to detect toxicity. One month later, the patient felt much better; he was experiencing less anxiety, he required fewer units of insulin to control his blood glucose level, and the skin lesions had improved. Two months after commencement of methotrexate therapy, corticosteroid treatment was stopped, and the methotrexate dosage was increased to 7.5 mg per week. By the sixth month of this particular treatment with methotrexate, the patient’s skin lesions showed a spectacular improvement (figure 2). Skin slits performed at that time revealed a bacteriological index of 1+.

**Discussion.** Type 1 leprosy reactions are usually seen in the early stages of leprosy therapy, but they can also be seen when there is an improvement in the host’s immunity, even if therapy has not yet been started. In these reactions, there is an increase of the level of proinflammatory cytokines, mainly TNF-α, IL-1, IL-2, IL-4, IL-8, IL-10, IL-12, and INF-γ [4, 5].

Methotrexate is known to reduce the production of proinflammatory cytokines, decrease the expression of Th1 cytokines, and increase the expression of anti-inflammatory Th2 cytokines [6]. Other mechanisms of action are inhibition of purine synthesis, promotion of adenosine release, suppression of lymphocyte proliferation, neutrophil chemotaxis and adherence, and...
and reduction of serum immunoglobulin. However, the exact mechanism by which low doses of methotrexate modulate inflammation is under study.

Studies indicate that the most important actions of low-dose methotrexate treatment are its effects in increasing the adenosine level and in reducing the proinflammatory cytokine level while increasing the anti-inflammatory cytokine levels [6]. All of these effects may contribute to the benefit of methotrexate for the treatment of leprosy reactions; however, additional studies are needed to understand the role of this immunosuppressive drug in the treatment of such cases.

There are no cases reported in the literature of type 1 leprosy reactions treated with methotrexate, and there is only 1 reported case of type 2 leprosy reaction treated with low-dose methotrexate, with good clinical outcome [7]. One published case of erythema nodosum leprosum did not respond adequately to repeated courses of prednisolone, thalidomide, and pentoxifylline treatment, but it did respond to infliximab treatment; in that case, the symptoms had greatly diminished on the day after treatment was started [8]. On the other hand, there were 2 recently reported clinical cases of leprosy that developed after infliximab treatment for arthritis; after infliximab treatment was discontinued, both patients developed type 1 leprosy reactions. In one of these cases, the type 1 leprosy reaction occurred when the dose of methotrexate, which was also being given for arthritis, had been reduced [9].

In the search for additional regimens to treat leprosy reactions, other immunosuppressive drugs have been tested. Cyclosporine A has been used to treat type 2 leprosy reactions with variable results, and there was 1 case of a type 1 leprosy reaction that resolved after treatment with cyclosporine [10, 11]. Azathioprine, when given with prednisone, has been found to yield results comparable to those of prednisone alone for the treatment of type 1 leprosy reactions, and combination therapy is well tolerated in patients with a severe type 1 leprosy reaction [12]. Azathioprine can be used as a steroid-sparing agent. However, azathioprine acts slowly and has no effect on intraneuronal edema, and use of this agent is recommended only as an adjunct to corticosteroids [3]. Methotrexate has fewer adverse effects than these drugs. Other treatments, such as pentoxifylline and mycophenolate mofetil, have been used for type 2 reactions, but they did not provide a clinical benefit. Considering the literature and the case we have reported above, low-dose methotrexate (5–7.5 mg/week) could be an alternative agent for the treatment of type 1 leprosy reactions, especially when steroids cannot be used. However, more studies of this regimen are needed.

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References