Low-Dose Methotrexate Controls a Severe Form of Polyarteritis Nodosa

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 41-year-old white man presented with a 7-year history of erythematous papules, livedo reticularis, swelling, myalgias, arthralgias, Raynaud phenomenon, and very large, painful and progressive ulcers on the lower part of both legs (Figure 1). A skin biopsy specimen revealed polyarteritis nodosa (PAN) with fibrinoid necrosis of medium-sized vessels. The patient fulfilled 4 of the criteria for PAN (ie, weight loss >4 kg, livedo reticularis, myalgias, and characteristic histological picture). Also, he had an elevated erythrocyte sedimentation rate, leukocyte count (Figure 2), CD3+ cell count (pan-T cells) (3.5 × 10^9/L), CD3+CD4+ T-cell count (T-helper cells) (2.7 × 10^9/L), and antinuclear antibody titer (1:640, speckled pattern). Systemic prednisone therapy administered at dosages as high as 100 mg/d had little, if any, effect. The patient's intense pain could only be controlled with morphine derivatives.

THERAPEUTIC CHALLENGE

Polyarteritis nodosa is a necrotizing vasculitis of small and medium-sized arteries with a chronic course that needs effective long-term treatment with a favorable benefit-risk ratio, and our patient failed to respond to prednisone treatment.

SOLUTION

Treatment consisting of intravenous injections of methotrexate (25 mg/wk) was initiated. The skin lesions improved and the patient's pain ceased, so the morphine treatment could be discontinued. The ulcers completely healed within 6 months. The methotrexate therapy was not discontinued, but the dosage was adjusted based on disease activity (range, 10-35 mg/wk). The initial remission lasted for 15 months, at which time the patient again developed ulcers on the lower part of both legs despite ongoing methotrexate therapy (10-25 mg/wk), but the ulcers were much smaller, less deep, and not as painful as they were before methotrexate therapy was begun. To achieve healing, the dosage was adjusted (25-35 mg/wk). After 13 months, all the new ulcers had completely disappeared, and after 7 months the patient remained free of ulcers at a dosage of less than 25 mg/wk (Figure 3).

Routine laboratory parameters and lymphocyte subsets as determined by flow cytometry were regularly monitored once a week to once a month. Initially, the PAN-associated leukocytosis decreased during methotrexate therapy (Figure 2). Despite ongoing methotrexate treatment, the number of leukocytes increased after 18 months and was accompanied by worsening of the clinical picture (Figure 2). The treatment neither induced patho-
logic alterations of routine laboratory findings nor decreased circulating T-lymphocyte subsets. Histological examination of a liver biopsy specimen obtained after a cumulative methotrexate dose of 2.5 g revealed no hepatic abnormalities. An ultrasonogram of abdominal organs showed no hepatic fibrosis or cirrhosis. Dynamic hepatic scintigraphy after cumulative doses of 3.8 and 5.2 g revealed normal findings. With single weekly intravenous doses ranging from 10 to 35 mg, methotrexate therapy has controlled the patient’s PAN for more than 56 months. Despite a total cumulative dose of 5.5 g, the therapy was well tolerated, and we did not find any methotrexate-associated adverse effects.

Figure 2. Synopsis of leukocyte counts and polyarteritis nodosa (PAN) activity during low-dose methotrexate therapy with more than 56 months of follow-up (0 indicates no visible lesions; 1, few nodules, livedo reticularis, and no ulcer; 2, abundant nodules, small to medium-sized ulcer(s), livedo reticularis, and pain; and 3, abundant nodules, medium-sized to large ulcers without tendency to heal, livedo reticularis, and severe pain).

Figure 3. Scars and livedo reticularis but no visible ulcers on the lower part of the leg after a total methotrexate dose of 5491 mg.

Methotrexate has been successfully used in the treatment of different types of vasculitides, eg, Wegener granulomatosis, Takayasu arteritis, and giant cell arteritis, and has rarely been reported in patients with PAN. This article represents the first report of long-term low-dose methotrexate therapy in a case of severe cutaneous PAN.

There is evidence that an anti-inflammatory mechanism rather than immunosuppression is responsible for the effectiveness of the low-dose methotrexate regimen. This theory is supported by the lack of immunocompetent cell depression, which was confirmed in our case by the results of long-term monitoring of leukocytes and circulating T-cell subsets. The fact that a wide spectrum of vascular diseases, including PAN, demonstrate improvement during low-dose methotrexate therapy leads to the assumption that methotrexate may control a crucial inflammatory step or factor. Since the report of Segal et al, one of the major effects of low-dose methotrexate therapy seems to be the inhibition of interleukin 1 (IL-1) activity without alteration of either IL-1 synthesis or IL-1 secretion, a finding that has been confirmed by other researchers. Previously, we demonstrated in an in vitro assay that methotrexate inhibited IL-1 binding to its cell surface receptor. Interleukin 1 plays a central role in inflammatory events and vasculitides. It activates endothelial cells to express adhesion molecules and to produce other pro-inflammatory cytokines, such as IL-6 and IL-8, and stimulates the chemotactic activity of neutrophils. Moreover, methotrexate inhibits leukotriene B4- and/or C5a–induced neutrophil and macrophage chemotaxis and reduces platelet activation factor–induced leukocyte–endothelial cell adhesion.

The case presented herein is interesting in several respects: (1) as has been established in cases of psoriasis and rheumatoid arthritis, our case shows that methotrexate therapy also has short- and long-term efficacy in PAN; (2) short-term treatment involves a low risk for the development of adverse effects, but even during long-term follow-up (>56 months) of methotrexate treatment, our patient did not develop immunosuppression...
or any other adverse reaction; and (3) disease activity runs in parallel with absolute peripheral blood leukocyte counts (Figure 2).

We presume that the clinical improvement noted was mediated by methotrexate's anti-inflammatory properties. Therefore, low-dose methotrexate therapy appears to represent an interesting alternative treatment strategy for managing this complex disease. Clinical trials will be necessary to confirm this observation in a larger group of patients.

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REFERENCES


Submissions

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Ctr, Inc, 14377 Woodlake DR, Suite 111, St Louis, MO 63017. Reprints are not available.