Case Report

Vasculitis Associated with the Use of Leflunomide

JEANNIE MacDONALD, TONI ZHONG, ADRIANA LAZARESCU, BING SIANG GAN, and MANFRED HARTH

ABSTRACT. Vasculitis as a complication of leflunomide therapy in the treatment of rheumatoid arthritis has been reported. We describe a case of acute necrotizing vasculitis following leflunomide therapy. Characteristics of this case and 4 cases in the literature suggest that vasculitis may be a rare but serious adverse effect of leflunomide therapy. (J Rheumatol 2004;31:2076–8)

Key Indexing Terms:
LEFLUNOMIDE VASCULITIS RHEUMATOID ARTHRITIS IgA NEPHROPATHY

Leflunomide, an isoxazole derivative, is a disease modifying antirheumatic drug (DMARD) that acts by blocking pyrimidine synthesis and inhibiting CD4 T cell proliferation. Its efficacy in the treatment of rheumatoid arthritis (RA) is well documented[1-3]. Reported adverse effects include severe diarrhea, hepatotoxicity, increases in blood pressure, alopecia, and various rashes[1-3]. There have also been several case reports of severe vasculitis[4-6], although this complication was not attributed to the drug in the published clinical trials. We describe a case of severe vasculitis in a patient with RA soon after the introduction of leflunomide, and review the evidence on the possible relation of the drug to this complication.

CASE REPORT

A 66-year-old woman presented in the rheumatology outpatient clinic in May 2003 with widespread ulcerating skin lesions. She had severe, erosive, nodular RA that had started in 1988, and had previously been documented as rheumatoid factor (RF) positive. Previous treatments with intramuscular gold compounds and methotrexate had failed to control her synovitis. She had been treated only with nonsteroidal anti-inflammatory agents for most of the previous year, until leflunomide 20 mg/day had been started in March 2003. There had been no other preceding illness before leflunomide was started. After about 4 weeks, she developed numerous skin ulcerations in her upper and lower limbs and buttocks. This was associated with severe diffuse bilateral burning pain in her lower legs.

On examination, she was an anxious woman who walked stiffly. Pulse rate was 128/min, and blood pressure was 128/76 mm Hg. She had severe ulnar deviation at the metacarpophalangeal joints, and synovial thickening of the small joints of her hands and wrists. She had multiple rheumatoid nodules, which showed superficial ulcerations. There were widespread, well circumscribed necrotizing lesions, splinter infarcts, and palpable purpuric papules (Figure 1); there were necrotic, foul-smelling plaques overlying regions of ulcerated confluent papules and surrounding cellulitis mostly localized to the lower extremities. The largest infected bulla measured 7 × 5 cm and was on the posterior aspect of the ankle. Peripheral vascular examination showed intact bilateral pedal pulses and good capillary refill in the toes. On neurological examination she had decreased sensation to light touch distally in a symmetrical stocking-type distribution; motor function, however, was normal in the lower extremities.

Laboratory investigations revealed hemoglobin 140 g/l, white blood cell count 32.2 × 10^9/l with 84% neutrophils and 8% bands; platelet count was 308 × 10^9/l. Erythrocyte sedimentation rate was elevated at 89 mm/h. Electrolytes

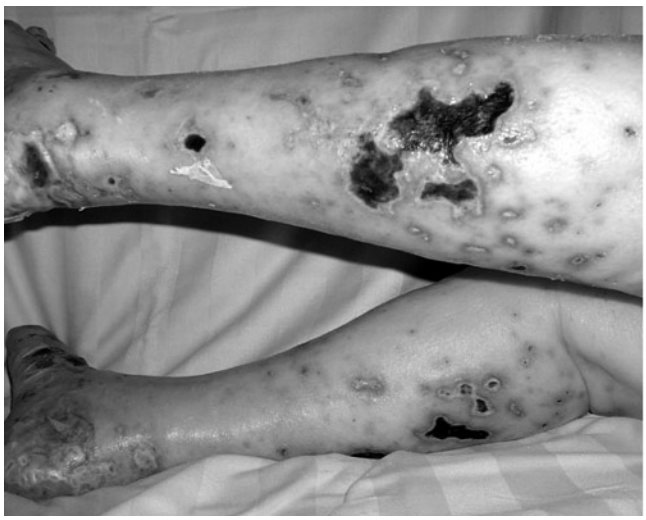

Figure 1. Posterior view of bilateral lower extremities showing the necrotizing vasculitic lesions, shortly after admission to hospital.

From the Department of Medicine, Division of Rheumatology, and Department of Surgery, Division of Plastic and Reconstructive Surgery, The University of Western Ontario, London, Ontario, Canada.

J. MacDonald, MD; T. Zhong, MD; B.S. Gan, MD, PhD, FRCSC, FACS, Division of Plastic and Reconstructive Surgery; A. Lazarescu, MD; M. Harth, MD, FRCPC, Division of Rheumatology.

Address reprint requests to Dr. M. Harth, The Arthritis Institute, St. Joseph's Health Centre, 268 Grosvenor Street, London, Ontario N6A 4V2, Canada. E-mail: manfred.harth@sjhc.london.on.ca

Submitted December 5, 2003; revision accepted March 10, 2004.

were within normal range, but both blood urea nitrogen (BUN) and serum creatinine were elevated at 13.9 mmol/l and 126 mmol/l, respectively (premorbid values were normal 5.6 and 81 mmol/l). Liver enzymes (AST and ALT) were normal, but the albumin was low at 23 g/l. Antibodies to hepatitis B and C were negative, as was the hepatitis B surface antigen. Antinuclear antibody (ANA) was positive at 1:640, with a homogenous pattern (no premorbid ANA determination was available), but anti-DNA antibodies and anti-extractable nuclear antigen antibodies were negative. Complement values (CH50, C3, C4) were normal. No circulating immune complexes could be detected. Interestingly, the RF test was negative. Antineutrophil cytoplasmic antibody (ANCA; anti-myeloperoxidase and anti-SR3) was negative, as were cryoglobulins. Immunoglobulins showed elevation of IgG to 14.3 g/l and IgA to 5.7 g/l, with normal IgM of 2.0 g/l; serum protein electrophoresis showed no abnormal bands. She had microscopic hematuria and proteinuria (> 3.0 g/l). The 24 hour protein excretion was 4 g. Premorbid urinalyses had been normal. Skin lesion cultures were positive for *Staphylococcus aureus* and *Enterococcus* species. Blood cultures were negative.

The patient was admitted to hospital. Leflunomide was stopped. She was started on cyclophosphamide orally 150 mg/day and prednisone 30 mg/day. The plastic surgery service was consulted for management of the cutaneous lesions. Intravenous clindamycin and ciprofloxacin were started, and the large infected and hemorrhagic bullae were deroofed and drained at the bedside. Topical metronidazole cream was applied to the ulcerated vasculitic regions and dressed with dry gauze twice daily.

The ulcers healed gradually, and her serum creatinine and BUN returned to normal values. One skin lesion was biopsied, but the specimen was obtained from a healed ulcerated site; the pathology was therefore noncontributory, showing only dermal scarring with a few patchy lymphocytic infiltrates.

She was discharged after 13 days of hospitalization and has been followed in the outpatient department. She continued therapy with cyclophosphamide, but prednisone was tapered to 15 mg/day. She continued to have proteinuria and microscopic hematuria and was therefore referred to a nephrologist, who performed a renal biopsy in October 2003. The biopsy showed focal mesangial matrix expansion with slight increase of cellularity in the mesangium; there was patchy mild interstitial fibrosis and patchy mild chronic inflammation; electron microscopy showed patchy fusion of the foot processes, with variable thickness of the basement membrane and electron-dense deposits in the mesangium. There was no evidence of vasculitis or crescent formations. Immunofluorescent studies showed strong IgA positivity in the mesangium, and weak C3 and IgM positivity in the glomeruli. The features were consistent with IgA nephropathy.

The ulcers continued to improve with daily dressing changes and abundant granulation tissue developed. The patient was offered skin grafting but declined. Currently the ulcers are clean and continue to decrease in size on a daily dressing regimen.

DISCUSSION

We have described a patient with RA who developed a severe necrotizing vasculitis shortly after she started leflunomide. She had a persistent leukocytosis, microscopic hematuria and proteinuria (serum creatinine and urinalysis had been normal before treatment), and symptoms suggesting a peripheral neuropathy (burning leg pain and decreased sensation to touch). She responded to a variety of measures including cessation of the drug, surgical debridement, and immunosuppressive therapy. It could be argued that we should also have used cholestyramine to speed up the elimination of leflunomide, as reported in one case[5]. She had a positive ANA, but showed no other immunologic abnormalities; although her records had stated that she was RF positive, we were unable to verify this.

There are 4 other reported cases of vasculitis with leflunomide therapy[4-6]. Their features and those of our patient are summarized in Table 1. Duration of leflunomide therapy before the onset of clinical evidence of vasculitis ranged between one and 12 weeks. The skin lesions described were necrotic in 4 cases ([4,5] and this case). Two cases had renal involvement ([5] and this case), both consistent with IgA nephropathy[5]. One case had symptoms suggestive of a radicular neuropathy[4], whereas our patient had symptoms suggestive of peripheral neuropathy. Skin biopsies established leukocytoclastic vasculitis in 2 cases[4,5]. In one case deposits of C3 and fibrinogen but not immunoglobulins were seen in the skin lesions, and C3 and IgA in the renal lesion[5]. Unfortunately, in our case we obtained a skin biopsy too late in a healed lesion. All patients were treated by withdrawing leflunomide, and in 4 cases steroids plus immunosuppressive drugs were given ([4,5] and this case). In one case the patient was rechallenged with leflunomide and redeveloped vasculitis[6]; eventually the patient was maintained on a low dose of the drug.

It is possible that there were other causes of vasculitis than leflunomide in our case or those reported in the literature. Vasculitis does occur as a complication of RA[7]. It is usually seen in seropositive patients, and is frequently associated with low complement levels and circulating immune complexes[7]. Renal involvement is unusual[7]. IgA nephropathy, seen in 2 cases of vasculitis associated with leflunomide, may be primary or secondary[8]. RA, other inflammatory arthritides, and several types of vasculitis can be associated with IgA nephropathy[8]. Interestingly, Bruyn, *et al* have recently reported a nephritis associated with antiglomerular basement membrane antibody in a patient with RA treated with leflunomide[9].

Table 1. Summary of cases of leflunomide-associated vasculitis.

Case	Age, Sex	Immunology	Prior Exposure to Leflunomide	Vasculitic Lesions	Outcome
1[4]	51 F	RF pos	1 mo	Necrotic lesions, feet, nose, ears	Persistent vasculitis; died
2[4]	58 M	RF pos	4 wks	Purpura on legs, necrotic lesions legs & feet	Persistent vasculitis; died
3[5]	51 M	RF ?; aCL pos (IgM) ANA neg ANCA neg	1 wk	Hemorrhagic bullae on feet eroding to ulcers	Improved
4[6]	50 M	RF pos ANA neg ANCA neg	3 mo	Vasculitic lesions on fingertips	Improved; continued on small doses
Present case	66 F	RF pos ? ANA pos	4 wks	Necrotic ulcers, palpable purpura	Improved

RF: rheumatoid factor, IgM: immunoglobulin M, aCL: anticardiolipin antibody, ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody.

Another possibility in our case and those reported is that these were cases of coincidental, ANCA-associated vasculitis. However, ANCA was negative in our patient and one other report[5]. Vasculitis has been reported as occurring in 0.6% of one large series of RA patients receiving leflunomide, but was not clearly attributed to the drug[1,6]. Brogan and Olsen recently reviewed drug-induced rheumatic syndromes, including drug-induced ANCA-positive vasculitis, and did not mention leflunomide as one of the implicated drugs[10]. At this time, pending additional evidence, a causal association of leflunomide with vasculitis can only be regarded as suspect rather than established.

REFERENCES

1. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomized, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259-66.
2. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology Oxford 2000;39:655-65.
3. Cohen S, Cannon GW, Schiff M, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis Rheum 2001;44:1984-92.
4. Bruyn GA, Griep EN, Korff KJ. Leflunomide for active rheumatoid arthritis [letter]. Lancet 1999;353:1883.
5. Holm EA, Balslev E, Jemec GB. Vasculitis occurring during leflunomide therapy. Dermatology 2001;203:258-9.
6. Chan AT, Bradlow A, McNally J. Leflunomide induced vasculitis — a dose-response relationship [letter]. Rheumatology Oxford 2003;42:492-3.
7. Vollertsen RS, Conn DL. Vasculitis associated with rheumatoid arthritis. Rheum Dis Clin North Am 1990;16:445-61.
8. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med 2002;347:738-48.
9. Bruyn GA, Veenstra RP, Halma C, Grond J. Anti-glomerular basement membrane antibody-associated renal failure in a patient with leflunomide-treated rheumatoid arthritis [letter]. Arthritis Rheum 2003;48:1164-5.
10. Brogan BL, Olsen NJ. Drug-induced rheumatic syndromes. Curr Opin Rheumatol 2003;15:76-80.