

Sensory Neuropathy Revealing Necrotizing Vasculitis During Infliximab Therapy for Rheumatoid Arthritis

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ABSTRACT. We describe 2 patients with severe erosive rheumatoid arthritis and rheumatoid vasculitis, respectively, in whom infliximab therapy was associated with peripheral neuropathy due to necrotizing vasculitis in one patient and to progression of preexisting mononeuritis multiplex in the other. (*J Rheumatol* 2004;31:2079–81)

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RHEUMATOID VASCULITIS
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INFLIXIMAB
ANTI-TUMOR NECROSIS FACTOR

Rheumatoid vasculitis is an uncommon but potentially serious complication of rheumatoid arthritis (RA). The clinical prevalence is low, about 1% to 5% of patients with RA, although post-mortem studies have found higher prevalences of about 25%.¹ Blood vessels of all sizes may be affected, but predominant involvement of the small arteries is a characteristic feature of rheumatoid vasculitis. The most common and mildest clinical manifestations are small infarcts along the nail beds. Less frequently, involvement of small or medium-size arteries leads to peripheral neuropathy or more severe organ failure.²

Treatment of severe rheumatoid vasculitis usually relies on high dose corticosteroids combined with cytotoxic drugs, most notably cyclophosphamide, which has been found effective.¹ More recently, open studies have suggested that inhibition of tumor necrosis factor (TNF- α) may be effective in various refractory vasculitides such as Wegener's granulomatosis, cryoglobulinemia associated vasculitis, Behçet's disease, and rheumatoid vasculitis.^{3–5} Nevertheless, cases of leukocytoclastic vasculitis have occurred during treatment with TNF inhibitors^{6–9}, and one case of infliximab induced mononeuritis multiplex has been reported¹⁰.

We describe 2 patients with severe erosive RA and rheumatoid vasculitis, respectively, in whom infliximab therapy was associated with peripheral neuropathy due to necrotizing vasculitis in one patient and to progression of preexisting mononeuritis multiplex in the other.

Case 1. A 41-year-old Caucasian woman had an 18-year his-

tory of severe erosive seropositive RA refractory to numerous disease modifying antirheumatic drugs (DMARD) including intramuscular gold, salazopyrine, methotrexate, cyclosporine, and 10 mg prednisolone per day. Infliximab (3 mg/kg) and methotrexate (7.5 mg weekly) started in July 2001 produced dramatic improvement of the joint pain and synovitis within 1 month. In April 2002, after the 6th intravenous infliximab infusion, she reported dysesthesia in the distribution of the left peroneal nerve, while her RA was in remission. Clinical examination revealed hypoesthesia in the anterolateral part of the left leg. No motor deficiency or other systemic organ involvement was noted. An electromyographic study of the lower limbs established the diagnosis of mononeuritis affecting the left peroneal nerve. Her erythrocyte sedimentation rate was 15 mm/h. She had positive latex (80 IU/ml; normal 10 IU/ml) and Waaler-Rose (64 IU/ml; normal 30 IU/ml) tests. Investigations for antineutrophil cytoplasmic antigen, anti-DNA antibody, and serological hepatitis markers were negative. The peripheral blood eosinophil count was normal, serum C3 was normal, and C4 was slightly decreased (0.10 g/l). Serum creatinine and urine sediment were normal. Biopsy specimens were taken from the superficial peroneal nerve and peroneus brevis muscle, frozen, and embedded in paraffin. Examination of the muscle specimens stained with hematoxylin-eosin and trichrome disclosed Wallerian-like degeneration and mild neurogenic atrophy with no myelinated nerve fiber loss. An arteriole showed a parietal inflammatory infiltrate and partial obliteration of the lumen by fibroid necrosis (Figure 1). These results were consistent with peripheral neuropathy related to necrotizing vasculitis.

The infliximab was stopped and intravenous steroid pulse therapy (250 mg methylprednisolone for 3 days) was started, followed by 1 mg/kg/day of oral prednisone for 1 month. The prednisone was then tapered. Four months later, the neurological examination was normal and she reported no paresthesia. The joint involvement remained quiescent. A followup

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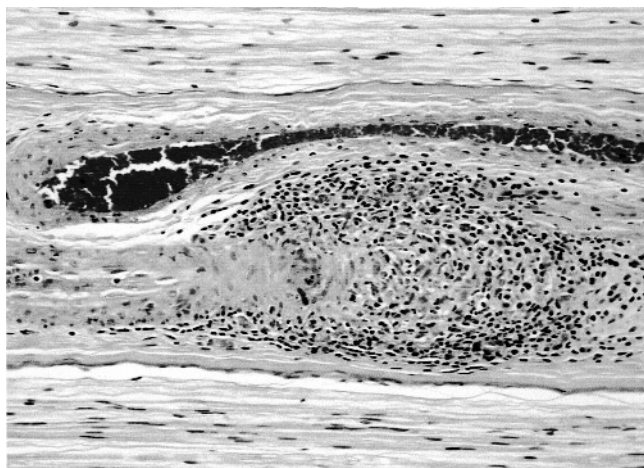


Figure 1. Partial necrotizing arteritis of a small artery with mild inflammatory infiltration of the arterial wall. The neighboring vein is unaffected (H&E; original magnification $\times 20$).

electromyographic study showed normal findings, in particular for the peroneal nerve.

Case 2. This patient was a 48-year-old Caucasian woman with erosive and seropositive RA of 5 years' duration refractory to several agents including hydroxychloroquine, salazopyrine, and methotrexate. In February 2002, she suddenly developed asymmetric hypoesthesia in the lower limbs secondary to sensory mononeuritis multiplex, confirmed by an electromyographic study. Clinically, the right peroneal nerve was predominantly involved. A neuromuscular biopsy of the right leg revealed neuronal necrotizing vasculitis. Her tests were negative for antinuclear antibody and antineutrophil cytoplasmic antigen. She had positive latex (160 IU/ml; normal 10 IU/ml) and Waaler-Rose (640 IU/ml; normal 30 IU/ml) tests. Intravenous steroid pulses (250 mg methylprednisolone for 3 days) followed by intravenous cyclophosphamide therapy (500 mg/m²) were given. After the 6th infusion, her neurological status appeared stable by clinical and electromyographic criteria, and the cyclophosphamide was stopped in July 2002. Nevertheless, her arthritis remained uncontrolled despite prednisone (20 mg/day) and add-on leflunomide (20 mg/day). Infliximab was added in March 2003. Eight hours after the first infusion, she complained of paraesthesia in her left leg, where she had not experienced symptoms previously, and of rapid extension of the hypoesthesia in her right leg. Examination revealed livedo of the lower limbs and previously unrecorded sensory loss in the distribution of the left peroneal nerve. Because these clinical events were consistent with infliximab induced progression of the preexisting mononeuritis, infliximab therapy was discontinued. Three additional cyclophosphamide injections were given, and the prednisone dosage was increased to 1 mg/kg. Followup investigations 3 months later showed slight improvements in the livedo and sensory neuropathy.

DISCUSSION

Peripheral nervous system involvement is a distinctive clinical feature of rheumatoid vasculitis. In addition to vascular lesions and inflammatory infiltrates, neuropathologic studies show axonal degeneration and fiber loss, presumably caused by nerve ischemia secondary to damage to the vasa nervorum. Mononeuritis and mononeuritis multiplex are the main clinical manifestations, whereas sensorimotor neuropathy is less common¹¹⁻¹³.

TNF- α inhibition has shown promise for the treatment of vasculitis, and several reports of beneficial effects in a variety of vasculitides have been published. Nevertheless, autoimmune-like adverse effects of the TNF- α inhibitors etanercept and infliximab in patients with RA have included lupus-like syndrome¹⁴, accelerated nodulosis^{15,16}, and leukocytoclastic vasculitis^{6-9,10}.

The temporal relationship in our patients between the onset or progression of neuronal vasculitis and the initiation of infliximab therapy strongly suggests that TNF- α inhibition may have contributed to trigger or worsen the vasculitis. Nevertheless, we cannot definitely exclude the development of vasculitis as a *de novo* phenomenon or a simple progression of disease in our patients. However, the improvement in paresthesia and electromyographic abnormalities noted after discontinuation of infliximab supports the hypothesis of a drug induced vasculitis. Because rheumatoid vasculitis is a serious disease, rechallenge with TNF- α inhibitors was not performed.

The pathophysiology of vasculitis is complex and incompletely understood. Vascular inflammation and blood vessel damage result from the release of proinflammatory cytokines and upregulation of adhesion molecules, which in turn increase vascular permeability, hemorrhage, and necrosis¹⁷. Various mechanisms might lead TNF- α inhibitors to promote rheumatoid vasculitis. In patients with leukocytoclastic vasculitis, anti-drug antibodies or autoantibodies produced during TNF- α therapy may form immune complexes that may deposit in the walls of small vessels, causing vasculitis^{6,9,10}. Our data do not support a role for autoantibodies in peripheral nerve vasculitis, as tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative in both patients. Other hypothetical mechanisms for infliximab induced vasculitis include changes in the T cell cytokine profile, elevation of nuclear antigen levels in the blood due to increased apoptosis of cells targeted by TNF- α inhibitors, and an increase in the immunogenic load due to downregulation of C-reactive protein by TNF- α inhibitors^{10,15}.

Although more clinical data are required to define clear causality, our data suggest that infliximab should be added to the list of agents associated with drug induced vasculitis in patients with RA.

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