Case Report

Rheumatoid Vasculitis Treated with Infliximab

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ABSTRACT. We describe a patient with rheumatoid vasculitis (RV) who showed a good response to anti-tumor necrosis factor-α therapy. TNF-α antagonists should be considered as treatment in systemic RV, especially in patients who do not respond to immunosuppressive drugs or who have contraindication for such treatment. (J Rheumatol 2005;32:1607–9)

Key Indexing Terms:
RHEUMATOID VASCULITIS INFLIXIMAB

Rheumatoid vasculitis (RV) is an uncommon complication of rheumatoid arthritis (RA) and is associated with increased morbidity and mortality[1]. The incidence of RV has declined since the 1980s, probably due to the more effective management of RA and decreasing nicotine abuse[2]. Cutaneous involvement is the most frequent clinical feature and can manifest as purpura, petechia, and/or hemorrhagic blisters[3]. In addition, vasculitis of the vasa nervorum may cause peripheral neuropathy[4]. Recommended immunosuppressive therapy for systemic RV consists of corticosteroids in combination with cyclophosphamide[1,5].

Currently, patients with active and longstanding RA who show incomplete response to disease modifying antirheumatic drugs (DMARD) can be treated successfully with tumor necrosis factor-α (TNF-α) antagonists. As only a small number of patients with RV have been treated with anti-TNF-α, the usefulness of these antagonists in RV is unclear. We describe a patient with histologically proven RV who responded favorably to such treatment.

CASE REPORT

In 2003 a 70-year-old patient with a longstanding rheumatoid factor (RF) positive, nodular, erosive RA was admitted because of petechia on both hands. In addition, he had sensory disturbances of his left foot and minimal joint complaints.

He had had RA since 1969 for which he had been treated with hydroxychloroquine, penicillamine, salazopyrin, and gold and since 1993 with methotrexate (MTX). Because of erosive destruction of the elbows he had received total joint replacements on both sides. A cervical slip (4 mm) was documented but did not result in neurological symptoms. In the past he had suffered recurrent transient ischemic events, and a modest sensory polyneuropathy was diagnosed in 1993. When he developed skin ulcers, in 1998, the tentative diagnosis of RV was made on clinical grounds. He was treated successfully with prednisone 60 mg/day. After the prednisone dose was tapered to 15 mg daily the ulcers relapsed. Consequently, the prednisone dose was increased and azathioprine 150 mg daily was added. Despite this treatment, the ischemic and painful skin defects on the right leg did not heal, and finally an amputation of the right lower leg was performed in 1999. Thereafter the prednisone dose was tapered and the azathioprine was stopped.

On admission, he was using the following medication: MTX 17.5 mg per week, folic acid, omeprazole, acetylsalicylic acid, acetaminophen, codeine, enalapril, alendronate, nifedipine, and ibuprofen.

Clinical examination revealed multiple petechia, especially localized at both hands. Arthritis of the metacarpophalangeal joints 2, 3, and 5 and the proximal interphalangeal joints 2 and 3 of his left hand was observed. Neurological examination revealed a foot drop and sensory loss on the dorsum of the left foot and shin; in addition the left Achilles tendon reflex was absent and there was minimal weakness of the intrinsic muscles of the hands.

Laboratory evaluation revealed a sedimentation rate of 25 mm/h, hemoglobin 8.3 mmol/l, white blood cell count 9.9 × 10^9/l, and thrombocytes 191 × 10^9/l. Serum creatinine and urine sediment were normal. RF (IgM) levels were 200 U/ml. Antinuclear antibodies and antibodies to antiextractable nuclear antigens were negative.

Neurophysiologic examination (nerve conduction studies and electromyography) showed severe axonal loss of the left peroneal nerve without evidence of pressure neuropathy at the caput fibulae. In addition, moderate axonal involvement of the left tibial nerve and the right median and ulnar nerves was observed. A working diagnosis was made of a vasculitic mononeuropathy of the peroneal nerve, superimposed on a preexistent polyneuropathy. A biopsy of the musculus quadriceps femoris showed vasculitis of the artery, with dense mononuclear cell infiltrate in the vessel wall and fibrinoid necrosis (Figure 1). The muscle fibers were without abnormalities.

After the diagnosis of RV with cutaneous and neural involvement, infliximab 200 mg (at Weeks 0, 2, and 6 and then every 8 weeks) was added to MTX therapy. After 5 months all petechia had disappeared and the peroneal nerve mononeuropathy was improved both clinically (increased strength of the anterior tibial muscle) and neurophysiologically (increased amplitude of the anterior tibial compound muscle action potential). There were no signs of arthritis. More than one year later he is still treated with infliximab in combination with MTX.

DISCUSSION

RV is an important and serious complication of longstand-

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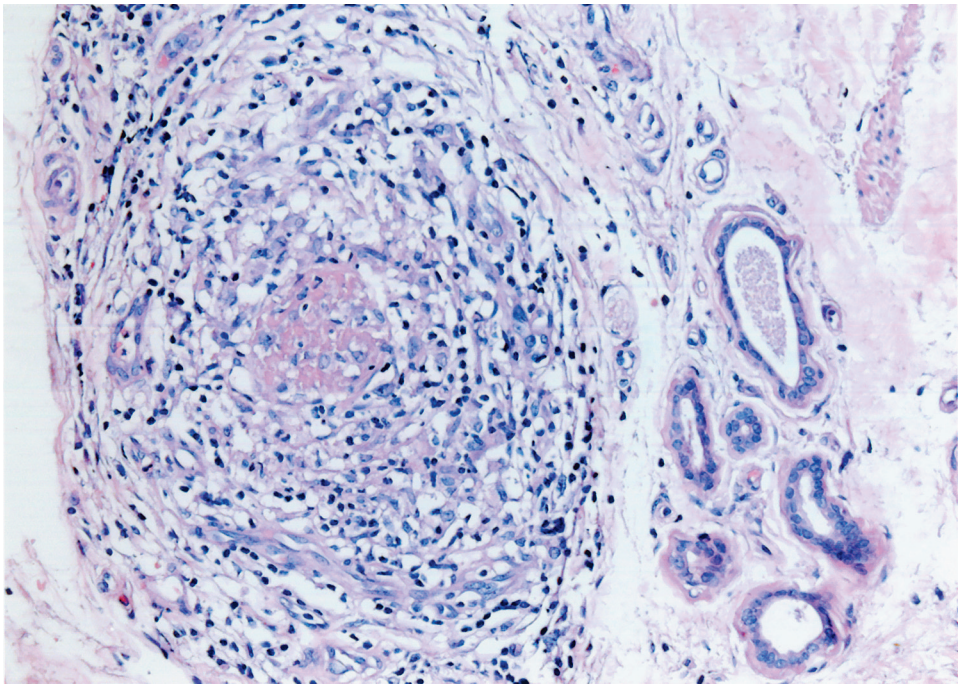

Figure 1. Sections of the biopsy taken from the musculus quadriceps femoris showed a blood vessel with destruction of the wall, infiltration of predominantly lymphocytes and macrophages, and obliteration of the lumen with the presence of fibrinoid necrosis. Further sectioning revealed that the thin vessel was a small-muscle artery (H&E stain, original magnification × 20).

ing RA[1]. Fortunately, the incidence of RV has declined during the last decades, probably due to improvement in the pharmacological treatment available for RA patients and the changes in tobacco smoking habits[2]. As systemic RV can be life-threatening, intensive immunosuppression such as high dose prednisone in combination with cyclophosphamide has

Table 1. Case reports of patients with rheumatoid vasculitis or RA associated pulmonary fibrosis successfully treated with anti-TNF-α.

Author	Clinical Finding	Previous Treatment	Anti-TNF-α Therapy
Richter[8]	Mononeuritis	MTX, ASA, HCQ, CS*	Etanercept 25 mg twice a week added
den Broeder[10]	Petechia	Low dose CS*	Lenercept 50 mg every 4 weeks
Garcia-Porrua[7]	Mononeuritis	CYC, CS: ineffective	Infliximab 3 mg/kg every 8 weeks, MTX
Vassallo[12]	RA associated pulmonary vasculitis	CS, HCQ, LEF*	Infliximab 3 mg/kg every 8 weeks added
Bartolucci[11]	Ulcers	CYC, CS: ineffective	Infliximab 5 mg/kg every 8 weeks
Bartolucci[11]	Mononeuritis + ischemia	CYC, CS: ineffective	Infliximab 5 mg/kg every 8 weeks
Unger[9]	Serositis + inflammatory syndrome	CYC, CS, PE: ineffective	Infliximab 3 mg/kg every 8 weeks
Unger[9]	Ulcers	CYC, CS: ineffective, side effect	Infliximab 3 mg/kg every 8 weeks
Unger[9]	Ulcers	Cyclosporine: ineffective CYC: leukopenia	Infliximab 3 mg/kg every 8 weeks
Our case	Mononeuritis + petechia	MTX*	Infliximab 3 mg/kg every 8 weeks added

ASA: salazosulfapyridine; CS: corticosteroids; CYC: cyclophosphamide; HCQ: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; PE: plasma exchange. * Maintenance therapy.

been advocated[1,5]. However, this therapy is associated with toxicity.

The antirheumatic drug infliximab was first introduced for the treatment of Crohn's disease and RA. Later, these drugs were labeled for psoriasis, ankylosing spondylitis, and psoriatic arthritis. Small and uncontrolled studies suggested that the TNF-α blocking agents are successful in different kinds of vasculitis syndromes. Recently, investigator-driven studies suggested the efficacy of TNF-α antagonists in a variety of systemic rheumatic diseases[6]. These included Behçet's disease, Churg-Strauss syndrome, polyarteritis nodosa, and giant cell arteritis. Even diseases such as Wegener's granulomatosis and sarcoidosis have been reported to be responsive to the TNF-α monoclonal antibody infliximab[6].

Including our case, the literature describes a total of 9 patients with RV and one patient with RA-associated pulmonary fibrosis who were treated successfully with TNF-α blocking agents[7-12] (Table 1). In 6 patients the initial treatment with cyclophosphamide was ineffective and the authors switched to anti-TNF-α. In 4 patients, anti-TNF-α was added to the maintenance therapy. The clinical response was good in all patients treated with infliximab (n = 8), as well as in 2 patients receiving the TNF-α-binding fusion proteins etanercept and lenercept. In contrast, one patient with progression of preexisting (RV related) mononeuritis during infliximab therapy after initial therapy with corticosteroids and cyclophosphamide has been reported[13].

Use of TNF-α blocking agents is now widespread. Side effects are predominantly injection site, infusion related reactions or infection[14]. Several patients were described who developed vasculitis during treatment with anti-TNF-α[15]. Most of these patients had skin disorders such as (vasculitic) rash and leukocytoclastic vasculitis. Others had neurologic involvement including mononeuritis and central nervous system vasculitis. A direct relationship between the vasculitis and the use of anti-TNF-α was unclear. Further investigation is required to define the possible link.

We describe the ninth patient with RV who showed a good response to anti-TNF-α therapy. TNF-α antagonists can be considered for treatment of systemic RV, especially in patients who do not respond to immunosuppressive drugs or who have a contraindication for such treatment.

REFERENCES

1. Turesson C, Matteson EL. Management of extra-articular disease manifestations in rheumatoid arthritis. Curr Opin Rheumatol 2004;16:206-11.
2. Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? Rheumatology Oxford 2004;43:920-3.
3. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. Br J Dermatol 2002;147:905-13.
4. Rosenbaum R. Neuromuscular complications of connective tissue diseases. Muscle Nerve 2001;24:154-69.
5. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med 1984;76:377-84.
6. Keystone EC. The utility of tumour necrosis factor blockade in orphan diseases. Ann Rheum Dis 2004;63 Suppl 2:ii79-ii83.
7. Garcia-Porrua C, Gonzalez-Gay MA. Successful treatment of refractory mononeuritis multiplex secondary to rheumatoid arthritis with the anti-tumour necrosis factor alpha monoclonal antibody infliximab. Rheumatology Oxford 2002;41:234-5.
8. Richter C, Wanke L, Steinmetz J, Reinhold-Keller E, Gross WL. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. Rheumatology Oxford 2000;39:1436-7.
9. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. Ann Rheum Dis 2003;62:587-8.
10. den Broeder AA, van den Hoogen FH, van de Putte LBA. Isolated digital vasculitis in a patient with rheumatoid arthritis: good response to tumour necrosis factor alpha blocking treatment. Ann Rheum Dis 2001;60:538-9.
11. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology Oxford 2002;41:1126-32.
12. Vassallo R, Matteson E, Thomas CF Jr. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. Chest 2002;122:1093-6.
13. Richette P, Dieude P, Damiano J, Liote F, Orcel P, Bardin T. Sensory neuropathy revealing necrotizing vasculitis during infliximab therapy for rheumatoid arthritis. J Rheumatol 2004;31:2079-81.
14. Fleischmann R, Yocum D. Does safety make a difference in selecting the right TNF antagonist? Arthritis Res Ther 2004;6 Suppl 2:S12-S18.
15. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. J Rheumatol 2003;30:2287-91.