

Refractory Polyarteritis Nodosa Successfully Treated with Infliximab

JAMAL AL-BISHRI, NICOLE le RICHE, and JANET E. POPE

ABSTRACT. We describe a woman with severe polyarteritis nodosa (PAN) with visceral involvement unresponsive to multiple immunosuppressive drugs. Infliximab treatment was very effective in this case. Infliximab may potentially be used as an alternative agent for the treatment of patients with PAN refractory to conventional therapy. (J Rheumatol 2005;32:1371–3)

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POLYARTERITIS NODOSA

INFLIXIMAB

We describe a woman with severe polyarteritis nodosa (PAN) with visceral involvement unresponsive to multiple immunosuppressive drugs. Treatment with infliximab was very effective in this case. Infliximab may potentially be an alternative agent for the treatment of patients with PAN refractory to conventional therapy.

CASE REPORT

A 33-year-old woman was initially seen by the rheumatology service in November 1995. Her history included chronic diarrhea, right lower quadrant abdominal pain, livedo reticularis, and polyarthralgia dating from 1991. She had been successfully treated with prednisone and had been well until August 1995, when her symptoms recurred. The musculoskeletal examination in November 1995 revealed bilateral plantar fasciitis, bilateral ankle synovitis, and livedo reticularis.

Over the next 3 months she was found to have hydronephrosis requiring bilateral stents. A biopsy of skin lesions done in February 1996 was consistent with PAN. In March 1996, she was admitted for a laparotomy and required a resection of part of the terminal ileum and ascending colon. The pathology report indicated vasculitis of small vessels and diagnosis of PAN. Sections from the terminal ileum at the proximal resection margin showed a patchy capillaritis within the muscularis propria. Overlying mucosa and lamina propria of the small bowel showed no specific pathological features, but a similar capillaritis was observed in the distal resection margin of the larger specimen. There was some increase in submucosal connective tissue, suggestive of previous ischemic change; however, the overlying mucosa showed no evidence of an acute inflammatory process. Sections taken randomly from the remainder of the specimens of large bowel revealed an ongoing inflammatory process involving the serosa, as well as an ongoing inflammatory reaction involving the small vessels and capillaries. Evidence of a healed arteritis was seen in some sections, as were occasional giant cells. The predominant cells involved in the vasculitis included neutrophils and eosinophils, as well as scattered plasma cells and lymphocytes. Focal fibrinoid change in the vessel wall was observed at

some points (Figures 1, 2, 3). In May 1996 the urinalysis showed proteinuria of 1 g/l. The diagnosis of antinuclear cytoplasmic antibody-negative PAN was made, fulfilling the ACR diagnostic criteria¹. Hepatitis B, hepatitis C, antinuclear antibody, lupus anticoagulant serology, and anticardiolipin antibody tests were negative. Russell viper venom time and RPR tests were not conducted.

She started therapy with intravenous (IV) pulse cyclophosphamide in June 1996, with a tapering dose of prednisone (50 mg/day), which had been started in May 1996. By the end of 1997, she had completed an 18 month course of IV cyclophosphamide (total dose 15 g). Although she improved, the gastrointestinal symptoms and arthralgias persisted. Despite an average dose of 30 mg prednisone per day she had persistent arthralgias and livedo reticularis. Over the following year, she developed painful erythematous-violaceous nodules with multiple ulcerations on her legs and progressive weakness and neuropathic pain of the lower extremities, confirmed as mononeuritis multiplex by nerve conduction study. The main clinical problems in 1998 were mononeuritis multiplex and vasculitic lesions on the legs with intermittent diarrhea.

Between 1998 and 2000 the patient had tried numerous treatments for PAN including 2 more courses of IV cyclophosphamide, IV immunoglobulin, methotrexate (MTX), azathioprine, and chronic high dose prednisone. Another IV cyclophosphamide treatment with concomitant pulse methylprednisolone was initiated in 2000, but resulted in no benefit. Indeed, livedo reticularis, vasculitic ulcers, and mononeuritis multiplex of the feet worsened to the point that the patient required a wheelchair. At that time, she also developed mononeuritis multiplex of the hands, hypertension, and a cardiomyopathy (left ventricular dysfunction confirmed by echocardiogram).

Following the failure of multiple medical treatments, including an investigational immunosuppressive, LF 15-0195 (which nearly cleared the livedo reticularis but caused fluid retention) the patient relapsed and was then prescribed 5 mg/kg infliximab in conjunction with MTX 15 mg/week and prednisone 30 mg/day in December 2000. She received infliximab at 0, 2, and 6 weeks and then every 8 weeks, and had a dramatic improvement, with healing of the ulcers by March 2002, just over 14 months after starting infliximab. The gangrenous ulcers on the legs healed rapidly and completely (Figures 3 and 4), and the mononeuritis multiplex improved. She is now walking with some difficulty and her prednisone has been reduced to 10 mg/day. At present, she is taking infliximab 300 mg given every 8 weeks.

DISCUSSION

Garcia-Porrua and Gonzalez-Gay have described a case of PAN in a patient with undifferentiated spondyloarthropathy that was successfully treated with infliximab, which result-

From the Division of Rheumatology, Department of Medicine, University of Western Ontario, London, Ontario, Canada.

J. Al-Bishri, MD; N. le Riche, MD, FRCPC, Associate Professor of Medicine; J.E. Pope, MD, MPH, FRCPC, Associate Professor of Medicine and Epidemiology and Biostatistics.

Address reprint requests to Dr. J.E. Pope, St. Joseph's Health Care London, 268 Grosvenor Street, Box 5777, London, ON N6A 4V2.

E-mail: janet.pope@sjhc.london.on.ca

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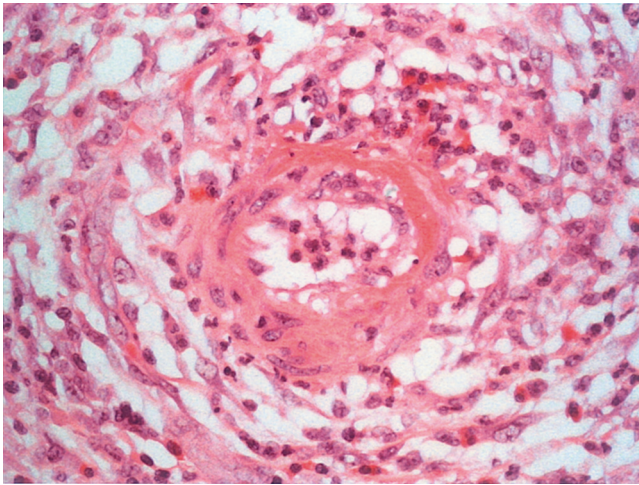


Figure 1. Small blood vessels with fibrinoid necrosis and inflammation (eosinophils, polymorphonuclear leukocytes, and chronic inflammatory cells) consistent with PAN in a pathological specimen of the bowel.

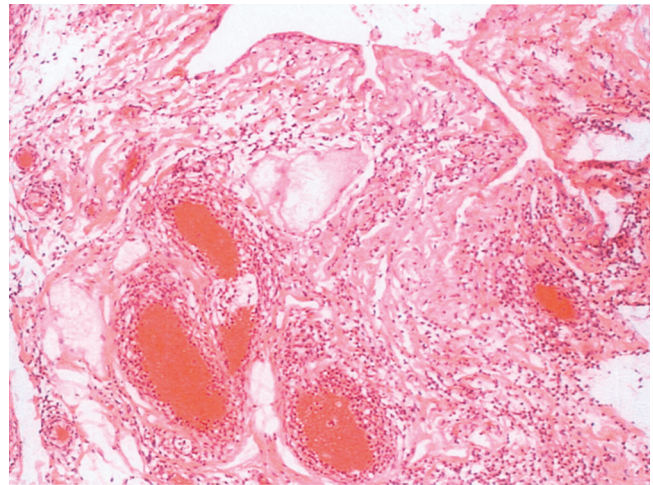


Figure 2. Small vessel vasculitis near the serosal surface of the intestine, consistent with PAN in a pathological specimen of the bowel.



Figure 3. Healed ulcers on the anterior aspect of the leg and marked decrease in livedo reticularis. Photograph was taken 14 months after start of infliximab therapy.



Figure 4. Healed ulcers on the posterior aspect of the leg and marked decrease in livedo reticularis. Photo was taken 14 months after infliximab initiation.

ed in symptom resolution by 18 months². The time to ulcer healing after initiation of tumor necrosis factor- α (TNF- α) blockade in this reported case was similar to the 14 months observed in our patient. Infliximab has been used to treat vasculitis³. The management of PAN, a vasculitis of small and medium size vessels involving the skin, kidney, peripheral nerves, gut, muscle, testes, heart, and occasionally lung, is based on the extent and rate of involvement of target tissues^{4,5}. Corticosteroid therapy has been shown to be beneficial in patients with limited or nonprogressive PAN. In cases that progress rapidly and involve the viscera, or that cannot be controlled with tolerable doses of prednisone, the addition of cytotoxic agents is necessary (e.g., cyclophosphamide, azathioprine, or MTX). When these agents fail, choice of treatment is difficult because of a lack of appropriately designed trials.

Endothelial cell activation is important in the development of vasculitis. Interleukin 1, interferon- γ , and TNF- α , cytokines that influence endothelial cell function, are elevated in the sera of patients with polyarteritis⁶. Infliximab, a chimeric monoclonal anti-TNF- α antibody, is an effective treatment for rheumatoid arthritis⁷ and other rheumatic conditions characterized by a chronic inflammatory state^{8,9}. The literature suggests that anticytokine therapy might be beneficial in vasculitis^{3,10-14}; however, to date only one other report has described the efficacy of anti-TNF- α inhibition (infliximab) in PAN².

We have described a woman with severe PAN with visceral involvement unresponsive to multiple immunosuppressive drugs. Infliximab treatment was very effective. Infliximab could potentially be used as an alternative agent for the treatment of cases of PAN refractory to conventional therapy.

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REFERENCES

1. Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088-93.
2. Garcia-Porrúa C, Gonzalez-Gay MA. Successful response to infliximab in a patient with undifferentiated spondyloarthritis coexisting with polyarteritis nodosa-like cutaneous vasculitis. *Clin Exp Rheumatol* 2003;21 Suppl 32:S138.
3. Lamprecht P, Voswinkel J, Lillenthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology Oxford* 2002;41:1303-7.
4. Valente R, Conn D. Polyarteritis-polyarteritis nodosa and microscopic polyangiitis. In: Dieppe P, editor. *Rheumatology*. London: Mosby International;1998:7.20.1.
5. Bacon PA. Therapy of vasculitis. *J Rheumatol* 1994;21:788-90.
6. Pall AA, Savage CO. Mechanisms of endothelial cell injury in vasculitis. *Springer Semin Immunopathol* 1994;16:23-37.
7. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932-9.
8. Van den Bosch F, Kruihof E, Baeten D, et al. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthritis: an open pilot study. *Ann Rheum Dis* 2000;59:428-33.
9. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumour necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346-52.
10. Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001;44:2933-5.
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. Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL. Treatment of intestinal Behcet's syndrome with chimeric tumour necrosis factor alpha antibody. *Gut* 2001;49:725-8.
13. Licata G, Pinto A, Tuttolomondo A, et al. Anti-tumour necrosis factor alpha monoclonal antibody therapy for recalcitrant cerebral vasculitis in a patient with Behcet's syndrome. *Ann Rheum Dis* 2003;62:280-1.
14. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. *Arthritis Rheum* 2001;44:1149-54.