INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. **The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail:jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Successful Treatment of Rheumatoid Vasculitis-Associated Foot-drop with Infliximab

To the Editor:

We read with interest of the experience of Richette and colleagues in the use of infliximab in rheumatoid arthritis (RA)[1], in which they describe the development of necrotizing vasculitis-associated sensory neuropathy in one patient and the deterioration of rheumatoid vasculitis-associated mononeuritis multiplex in another. This contrasts with our own recent experience of a patient with rheumatoid vasculitis who developed a mononeuritis of the left common peroneal nerve with foot-drop, resistant to 6 infusions of cyclophosphamide and high dose oral steroid, but resolving entirely after 6 doses of infliximab.

The patient was a 52-year-old woman with a 20 year history of erosive seropositive RA, which had been resistant to treatment with a range of disease modifying antirheumatic drugs over the years, including methotrexate, myocrisine, and D-penicillamine; she was then maintained on leflunomide 10 mg and prednisolone 20 mg daily. Her drug therapy had been unchanged for over a year, except for a gradual increase in her dose of steroid. She had a history of rheumatoid vasculitis, treated successfully with intravenous cyclophosphamide, but leaving her with a peripheral sensory neuropathy in both feet, with reduced sensation from mid-shin distally.

She presented 4 months before commencing infliximab therapy with left-side foot-drop that had developed over a few days. On examination, there was complete loss of power on dorsiflexion of the left foot. Nerve conduction studies revealed marked distal delay in the left common peroneal nerve (6.2 ms) and undetectable motor response. The rest of the neurological examination was unchanged. She received 6 infusions of 500 mg cyclophosphamide over 12 weeks, with 40 mg prednisolone daily and cotrimoxazole prophylaxis, without any improvement in her foot-drop.

Four months after her presentation she commenced infliximab (3 mg/kg), stopped leflunomide, and restarted methotrexate at a dose of 7.5 mg/week. The steroid dose was initially unchanged, but was gradually reduced to 5 mg daily once she reported significant clinical improvement in pain and stiffness with infliximab infusions. After the third infliximab infusion, there was a gradual return of left ankle dorsiflexion, and after the sixth infusion, power had returned to normal.

Despite the negative experience of Richette and colleagues, and other reports of the development of optic neuritis with infliximab treatment in RA[2], we suggest that the drug can offer benefits to at least some patients with rheumatoid vasculitis-associated mononeuritis.

DAVID J. ARMSTRONG, MD; MAURA T. McCARRON, MD; GARY D. WRIGHT, MD, Department of Rheumatology, Musgrave Park Hospital, Belfast, UK.

REFERENCES

1. Richette P, Dieude P, Damiano J, et al. Sensory neuropathy revealing necrotizing vasculitis during infliximab therapy for rheumatoid arthritis. J Rheumatol 2004;31:2079-81.
2. Ten Tusscher MPM, Jacobs PJC, Busch MJWM, de Graff L, Diemont WL. Bilateral anterior optic neuropathy and the use of infliximab. BMJ 2003;326:579.

Drs. Richette and Bardin reply

To the Editor:

We read with interest the letter of Dr. Armstrong and colleagues describing successful treatment of rheumatoid vasculitis-associated mononeuritis with infliximab. We would stress that our case report is not isolated. Several authors have described patients developing vasculitis during treatment with either infliximab or etanercept[1-6]. Most of the described cases were leukocytoclastic vasculitis, but Jarrett, *et al* also reported a patient with neurological manifestations[6]. Even if these cases suggest a relationship between tumor necrosis factor-α (TNF-α) blockade and vasculitis, the association is not definitive.

In contrast with this possible side effect, anti-TNF-α has been proposed for management of various systemic vasculitis, and dramatic improvements have been reported. In our opinion, it is still difficult to assess the role of TNF-α blockers in the management of vasculitis since reports have been mainly case reports or uncontrolled studies. A negative randomized placebo-controlled trial with etanercept in Wegener's granulomatosis was reported at the 2004 American College of Rheumatology meeting[7].

Finally, we would emphasize the need for caution in the use of anti-TNF-α agents for treatment of rheumatoid vasculitis. Guillevin, *et al* have suggested that TNF antibody use should be restricted to patients with vasculitis refractory to steroids and immunosuppressant agents[8]. Randomized controlled studies are required to clarify the role of anti TNF-α in the treatment of rheumatoid vasculitis.

It is important to recognize this potential side effect as, if confirmed, discontinuation of TNF-α inhibitors should be considered. This presumably rare side effect should not discourage the use of anti-TNF-α agents for the treatment of RA.

PASCAL RICHETTE, MD, PhD; THOMAS BARDIN, MD, Fédération de Rhumatologie, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France.

REFERENCES

1. Galaria NA, Werth VP, Shumacher HR. Leukocytoclastic vasculitis due to etanercept. J Rheumatol 2000;27:2041-3.
2. Livermore PA, Murray KJ. Anti-tumour necrosis factor therapy associated with cutaneous vasculitis. Rheumatology Oxford 2002;41:1450-2.
3. Cunnane G, Warnock M, Fye KH, Daikh DI. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum 2002;47:445-9.
4. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology Oxford

2002;41:116-7.
5. Mohan N, Edwards ET, Cupps TR, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. J Rheumatol 2004;31:1955-8.
6. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. J Rheumatol 2003;30:2287-91.
7. The WGET research group. The Wegener's Granulomatosis Etanercept Trial (WGET): Randomized, double-masked, placebo-controlled trial of etanercept for the induction and maintenance of remission [abstract]. Arthritis Rheum 2004;50 Suppl:S1719.
8. Guillevin L, Mouthon L. Tumor necrosis factor alpha blockade and the risk of vasculitis. J Rheumatol 2004;31:1885-7.

Infliximab Induced Chilblain Lupus in a Patient with Rheumatoid Arthritis

To the Editor:

We read with great interest the report by Louis, *et al*[1] on induction of autoantibodies during prolonged treatment with infliximab in 42 patients with inflammatory rheumatic diseases. In their study, no patient developed clinical manifestations of a new connective tissue disease. Nevertheless, some autoimmune disorders (lupus[2,3], demyelinating disease[4], diabetes mellitus[5], and vasculitis[6]) have been induced by tumor necrosis factor (TNF) blockade. Indeed, TNF-α plays an important role in regulating immune cell differentiation and function, thereby maintaining immune system homeostasis. Moreover, TNF-α blockers may interfere not only with the cytokine balance but with the whole immune response.

For Louis, *et al* the antibodies induced by anti-TNF-α were a normal response to an abnormal load of cellular antigens due to apoptosis and/or necrosis, or these autoantibodies predated the onset of a specific disease process. What should be done in the latter case, where there is lupus-like syndrome induction? In most reports, authors withdraw TNF blockers[2,7]. However, this raises 2 issues: Is withdrawal necessary even when clinical manifestations of lupus are mild? And is there a risk of exacerbation if the anti-TNF is maintained?

In this context, we describe a 55-year-old woman who developed chilblain lupus during treatment with infliximab and improved with addition of plaquenil. She presented with a 13-year history of severe rheumatoid arthritis (RA) and had been successfully treated by methotrexate and low dose oral prednisone (5–8 mg/day) for 10 years. Then, owing to lack of efficacy and progressive joint damage, infliximab was added to her treatment. At that time, immunological investigations showed positive rheumatoid factor but no antinuclear (ANA) or dsDNA antibodies. She improved rapidly, and prednisone and symptomatic treatments were withdrawn. Seventeen months after beginning infliximab, however, she presented with Raynaud's phenomenon on the hands and small ulcers on her fingers. Eight weeks later and while still receiving infliximab, her cutaneous lesions worsened. Examination revealed fissures and ulcers on the fingers and small violaceous papular lesions on the tip of the nose and on the lobule of the ears. There was no recurrence of synovitis. At that time, laboratory investigations revealed positive ANA (titer 1:32,000), antinucleosome antibodies (titer 13.2), but no dsDNA antibodies. The inflammatory variables remained stable (erythrocyte sedimentation rate = 17, C-reactive protein < 5).

Biopsies were taken from skin lesions on her fingers. Microscopic examination showed hyperkeratosis of the epidermis and perivascular lymphocytic infiltrates in the dermal portion, without signs of vasculitis (Figure 1). Direct immunofluorescence of the nonlesional skin was negative. The morphology and the microscopic aspect of these skin lesions were suggestive of chilblain lupus.

Since such chilblain lupus usually has a good prognosis and frequently abates with topical and symptomatic treatment, infliximab was maintained and plaquenil and calcium blocker were added even though the patient had immune disorders. The skin lesions and Raynaud's abated considerably within the following month, and no exacerbation of lupus was noted in the following 12 months. ANA titer was also decreased at the next infusion (1:8000).

Chilblains are cutaneous inflammatory lesions commonly occurring during cold and humid periods. Long-lasting chilblains can be either idio-

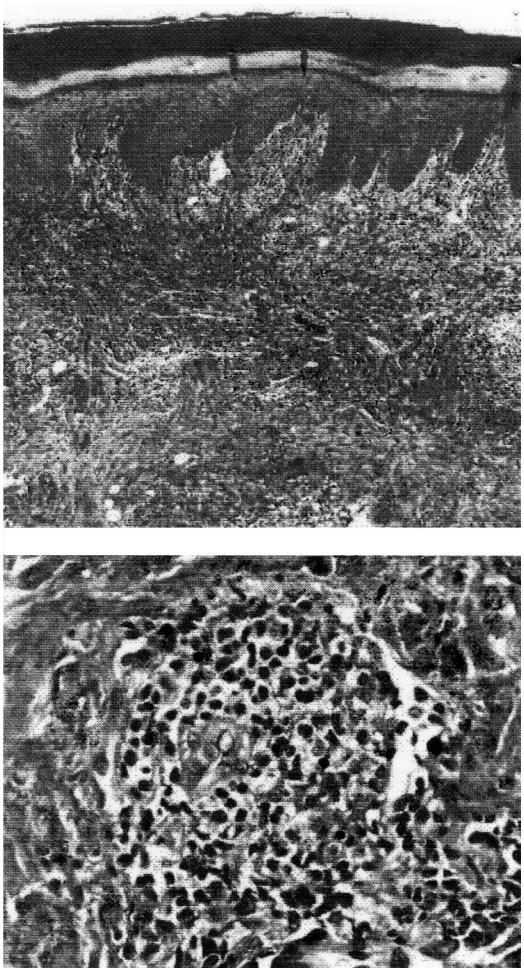

Figure 1. Micrographs suggestive of chilblain lupus. Upper panel: Hyperkeratosis of the epidermis and perivascular lymphocytic infiltrates in the dermal portion, without signs of vasculitis. Lower panel: Enlargement of perivascular lymphocytic infiltrates.

pathic and isolated, or associated with various connective tissue diseases, especially lupus. Indeed, chilblains can be the first manifestation of disease[8], but are rare in RA. In our patient, however, we do not think chilblain lupus was related to her RA. Chilblains are not commonly related to RA, and she was in RA remission taking infliximab therapy when manifestations occurred.

Another question is whether her condition could be considered "rhupus" syndrome. This hypothesis seems improbable, as she had no manifestation of clinical lupus and no antibodies to dsDNA prior to initiation of anti-TNF therapy. Thus, in view of the chronology of the chilblain lupus, the appearance of autoantibodies, and the beginning of anti-TNF treatment, we consider that the chilblain lupus was a side effect of infliximab. Interestingly, such chilblain lupus has previously been attributed to other medications such as terbinafine[9].

It is important to note that despite continuation of anti-TNF treatment, clinical lupus manifestations resolved with symptomatic treatment, and possibly the addition of plaquenil (although the level of autoantibodies did not vary significantly), and there has been no recurrence of lupus or a similar manifestation after one year of followup.

Therefore, in such a case of mild lupus-like syndrome occurring in patients with RA treated with TNF blockers, we suggest that treatment withdrawal may not be necessary, since the lupus manifestation may be managed with conventional therapeutics added to anti-TNF under strict control, as previously reported by Bleumink, *et al*[10].

CHRISTOPHE RICHEZ, MD; CHANTAL DUMOULIN, MD; THIERRY SCHAEVERBEKE, MD, PhD, Service de Rhumatologie, Groupe Hospitalier Pellegrin, CHU de Bordeaux, 6 place Amélie-Raba-Léon, 33076 Bordeaux Cedex, France. E-mail: christophe.richez@club-internet.fr

REFERENCES

1. Louis M, Rauch J, Armstrong M, Fitzcharles MA. Induction of autoantibodies during prolonged treatment with infliximab. J Rheumatol 2003;30:2557-62.
2. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet 2002;359:579-80.
3. De Rycke L, Kruithof E, Van Damme N, et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum 2003;48:1015-23.
4. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: by what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum 2001;44:1977-83.
5. Bloom BJ. Development of diabetes mellitus during etanercept therapy in a child with systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 2000;43:2606-8.
6. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. J Rheumatol 2003;30:2287-91.
7. Carlson E, Rothfield N. Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis [letter]. Aigner T [reply]. Arthritis Rheum 2003;48:1165-6.
8. Viguier M, Pinquier L, Cavelier-Balloy B, et al. Clinical and histopathologic features and immunologic variables in patients with severe chilblains. A study of the relationship to lupus erythematosus. Medicine Baltimore 2001;80:180-8.
9. Bonsmann G, Schiller M, Luger TA, Stander S. Terbinafine-induced subacute cutaneous lupus erythematosus. J Am Acad Dermatol 2001;44:925-31.
10. Bleumink GS, ter Borg EJ, Ramselaar CG, Stricker BHC. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology Oxford 2001;40:1317-9.

Book Review

Soft Tissue Rheumatology

Brian Hazelman, Graham Riley, Cathy Speed, editors. New York, NY: Oxford University Press, 2004. 568 pages, price $198.50 US.

Whether caring for patients with systemic disorders or looking at local problems, physicians who treat musculoskeletal disease often must evaluate and manage soft tissue problems. This text puts into focus the issues surrounding pain and dysfunction that result from problems with tendons, ligaments, bursae, menisci, intervertebral discs, and other tissues in and around the joint

The science of the soft tissues is effectively described, including their structure and individual roles in the maintenance of normal joint function. An excellent chapter deals with chronic pain and applies it to practical issues in musculoskeletal management. The approach is a classic one, going from the basic history and physical examination to the utility of various investigative tools. Sensitivity to the real world is exemplified by sections dealing with sports medicine and occupational disorders of soft tissues. Current management modalities are individually described, and the importance of the multidisciplinary approach is emphasized. The first 5 chapters deal with an overriding assessment of all issues. It is then in the final chapter that individual areas (the spine, the shoulder, the elbow and forearm, etc.) are discussed.

The organization of this volume is superb. It is detailed, and yet it is easy to find any topic of concern. Contributors include members of all disciplines who evaluate and treat musculoskeletal pain. Coming from a well-respected rheumatology research unit in Cambridge (UK), this book is clearly valuable to rheumatologists and indeed to any physician who participates in the care of patients with joint-associated pain and dysfunction. It is current in its science and is well supported by tables, graphs and pathologic photomicrographs. Though the scientific pages are complex, they are accessible to anyone with a basic knowledge of joint tissues and inflammation. The investigative and therapeutic portions are effectively written and offer the reader valuable information. This volume should be considered the definitive text in this area at present.

Jerry Tenenbaum, MD, FRCPC, FACP, Professor of Medicine, University of Toronto, Consultant Rheumatologist, Mount Sinai Hospital, University Health Network, Baycrest Geriatric Centre, Toronto, ON, Canada.