Infliximab induced chilblain lupus in a patient with rheumatoid arthritis.

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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Successful Treatment of Rheumatoid Vasculitis-Associated Foot-drop with Infliximab

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. Most of the described cases were leukocytoclastic vasculitis, but Jarrett, et al also reported a patient with neurological manifestations. 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 vasculitides, 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. 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. 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 presumptively rare side effect should not discourage the use of anti-TNF-α agents for the treatment of RA.

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REFERENCES

4. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology Oxford
Infliximab Induced Chilblain Lupus in a Patient with Rheumatoid Arthritis

To the Editor:

We read with great interest the report by Louis, et al. 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, demyelinating disease, diabetes mellitus, and vasculitis) 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. 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 and calcium blocker. 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-
pathic and isolated, or associated with various connective tissue diseases, especially lupus. Indeed, chilblains can be the first manifestation of disease, 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.

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 therapeutic agents added to anti-TNF under strict control, as previously reported by Bleumink, et al.

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REFERENCES


Book Review

Soft Tissue Rheumatology


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 few 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.

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