INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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Demyelinating Disease in a Patient with Psoriatic Arthritis and Family History of Multiple Sclerosis Treated with Infliximab

To the Editor:

Anti-tumor necrosis factor (anti-TNF) therapies represent a major advance in the treatment of inflammatory arthropathies, with an adequate safety profile, as shown in clinical trials. However, several potential risks such as predisposition to some infections (especially tuberculosis), heart failure, or development of lymphomas[1] have been uncovered in postmarketing reports. In addition, the development of demyelinating complications has been reported, although a definitive causal relationship has not been established[2-4]. Current guidelines recommend avoiding this therapy in patients with previous demyelinating disease. The question remains whether such caution should be extended to patients with first-degree relatives with multiple sclerosis (MS). We describe a patient with a family history of MS who developed central nervous system (CNS) demyelinating disease after commencing therapy with infliximab for psoriatic arthritis (PsA).

A 47-year-old woman with PsA presented to our hospital for the first time in March 2002. She had previously been treated with methotrexate and leflunomide but both had been discontinued because of intolerance. In October 2003 she developed a flare, with arthritis in multiple joints and a high level of functional impairment. Methotrexate 10 mg weekly and folic acid were started but there was inadequate response and poor tolerance; therapy with infliximab was then begun. One month later, she was completely asymptomatic. By June 2004, however, she reported paresthesias in the right side of the face. Over the ensuing days she developed bilateral decreased visual acuity, progressive paraparesis, paresthesias in the right upper limb, and clumsiness in the left upper limb. At that time she revealed that she had a sister with MS. Magnetic resonance imaging (MRI) studies showed several white matter lesions, hyperintense on T2 weighted scans, 2 of them located in the brain stem and 4 in the spinal cord; the majority of these lesions enhanced gadolinium and were felt to be consistent with demyelinating lesions (Figure 1). The cerebrospinal fluid (CSF) analysis yielded normal levels of glucose and proteins, with mild pleocytosis (10 lymphocytes/mm^3), intrathecal synthesis of IgG, and presence of oligoclonal bands. She was treated with boluses of methylprednisolone plus intravenous immunoglobulins (IVIG) with great improvement, although partial visual impairment and upper left limb clumsiness remained. In January 2005 she developed a new flare, with truncal ataxia and unstable gait; MRI revealed a new, enhancing lesion on the cervical spinal cord. She was again treated with high-dose steroids and IVIG, but this time with no improvement. She is now undergoing therapy with mitroxantone.

Although TNF-α may play a pathogenic role in MS, therapy with anti-TNF has not demonstrated any benefit, and indeed disease worsening has been reported[5]. The reasons underlying this paradox are unclear, but it has been suggested that as anti-TNF blockers cross the blood-brain barrier with difficulty, peripheral TNF blockade might in fact result in higher levels of TNF in the CNS[6].

The development of sporadic cases of demyelinating disorders in the context of anti-TNF therapy may relate to the presence of latent MS (patients with silent demyelinating plaques in the MRI). In addition, some investigators have pointed out the existence of a trait for MS. This would be a premorbid state in which predisposition for the development of this disease exists, although in contrast with latent MS, no demyelinating plaques would be observed in MRI; such patients, however, would have increased levels of antibodies against viral antigens, oligoclonal bands in the CSF, and increased vulnerability of the blood-brain barrier[7]. Although no definitive genetic markers have been described in MS, familial aggregation in this disease is well known, suggesting a genetic basis; siblings of patients with MS, therefore, carry a higher risk of predisposition for this disease[8,9]. Our patient developed a white matter disease, with CSF and MRI findings and a clinical course consistent with definite MS (there was time and space dissemination) in the context of a positive family history for the disease. Whether or not she had latent MS cannot be said, given that no imaging or CSF studies were carried out prior to the institution of infliximab therapy.

At present, the risk for this type of complication in patients treated with anti-TNF therapy and a family history of demyelinating diseases cannot be estimated. Although it is probably not very high, and indeed no similar cases have been reported so far, we suggest that family history of demyelinating disorders be carefully ascertained as a part of the pretreatment evaluation of patients considered for anti-TNF therapy, and that patients be properly informed of this potential risk; indeed, the British guidelines on the use of anti-TNF therapy have incorporated this concern in a recent update of the guidelines published in 2001[10]. Whether MRI examination should be undertaken in this type of patient before starting this therapy remains a matter of debate, but more data are needed to obtain a definitive answer.

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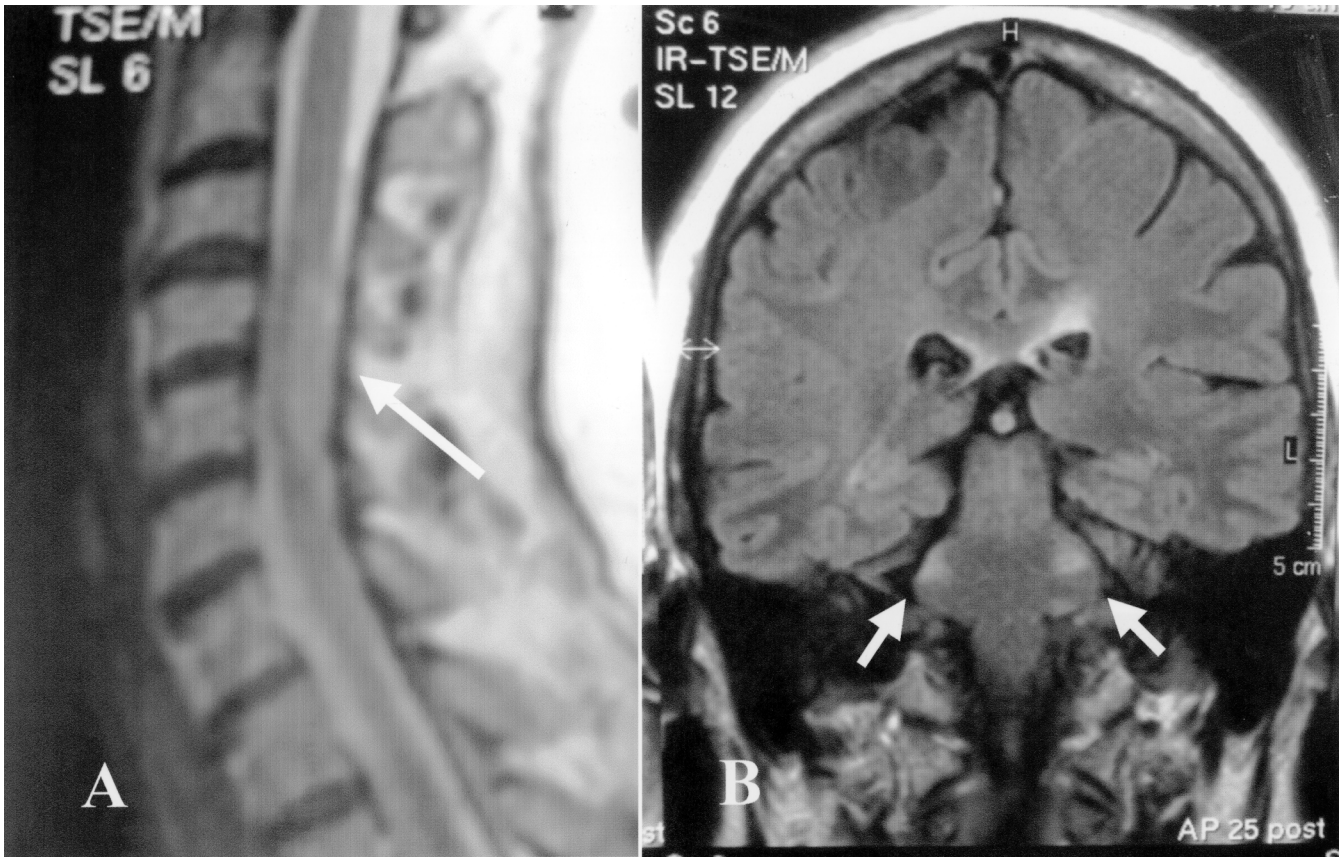

Figure 1. Magnetic resonance image showing hyperintense lesions in T2 consistent with demyelinating lesions at the cervical spinal cord (A, arrow) and brain stem at the level of cerebellar peduncles (B, arrows).

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Giant Cell Arteritis — The Methotrexate Debate Revisited

To the Editor:

Giant cell arteritis (GCA) is a common vasculitis that may result in significant morbidity including blindness if left untreated[1]. Corticosteroids, the mainstay therapy of GCA, are administered for prolonged periods, with substantial associated toxicity[2]. Numerous efforts have been made to minimize corticosteroid side-effects by utilizing steroid-sparing regimens. Methotrexate (MTX) was found to have such a sparing effect in one randomized controlled trial (RCT)[3], but that observation was not confirmed in other studies[2,4].

We describe 2 cases of GCA that initially developed in patients under treatment with MTX which was adequate to control their underlying rheumatoid arthritis (RA).

Case 1. An 80-year-old man with seropositive erosive RA had been followed in our rheumatology clinic for 5 years, with complete remission taking MTX 10 mg/week for the previous 2 years. One month prior to admission, he experienced occipital headaches, jaw claudication, malaise, and low grade fever (38°C). On admission, his temperature was 37.7°C. No active synovitis was detected. Nontender normally pulsating temporal arteries were evident. Laboratory tests revealed hemoglobin 11.6 g/dl; elevated C-reactive protein, 51 mg/l (normal 0–6 mg/l); and erythrocyte sedimentation rate (ESR) 80 mm/h. Funduscopic examination was normal. Temporal artery biopsy (TAB) was characteristic for GCA. Treatment with prednisone 60 mg/day resulted in prompt alleviation of symptoms and normalization of blood tests.

Case 2. A 73-year-old woman with seropositive RA had been followed in our clinic for 7 years, with complete remission taking MTX 10 mg weekly for the previous 3 years. Two weeks before admission to an internal medicine department in another hospital she began to suffer headaches and pain in both shoulders, accompanied by fever of 38.8°C. On admission, neither peripheral synovitis nor abnormal temporal arteries were noted. Laboratory tests showed ESR 96 mm/h; blood cultures were sterile; whole-body computerized tomography and gallium scans were unrevealing. Right TAB was normal. She was discharged with no specific diagnosis for the headaches.

Two weeks later she developed sudden left-eye blindness. Left TAB was diagnostic of GCA. Treatment with 60 mg prednisone resulted in rapid alleviation of fever, other systemic symptoms, and myalgias, but the blindness was irreversible.

Both patients continued MTX 7.5 mg/week and prednisone was reduced to 10 mg/day by 6 months, and they continued this regimen for one year after onset of GCA.

In 2001, Jover, *et al* raised renewed interest in the therapeutic role of MTX in GCA[3]. They found that 10 mg MTX weekly (or 15 mg weekly after a flare) decreased the cumulative prednisone dose needed to treat GCA and reduced the occurrence of relapses. However, 2 more recent trials arrived at a different conclusion[2,4]. Hoffman, *et al* evaluated 98 patients with GCA in a multicenter RCT: a regimen of 0.15–0.25 mg/kg MTX was not found to be corticosteroid-sparing. Potential weaknesses of that study included the use of alternate-day steroids after 4 weeks and the relatively early analysis of results[2]. The second RCT trial, by Spiera, *et al*, also showed no benefit for the adjunct use of MTX. That study has been criticized, however, for being underpowered (21 patients) and for the use of a low dose of MTX (7.5 mg weekly)[4].

Despite limited evidence, clinicians continue to use MTX as adjuvant therapy to corticosteroids in patients with relapsing or resistant GCA, extrapolating from the data presented above, as no other options, aside from anti-tumor necrosis factor (TNF) therapy, are at hand yet.

The cases we have described do not support the corticosteroid-sparing effect of MTX in GCA, and several issues remain to be considered. First, MTX is not intended as single therapy for GCA, and our patients were not treated with prednisone at the onset of GCA. Second, the controlled inflammation of RA is not an equivalent to the more substantial inflammatory burden of GCA. Third, in Jover's trial almost none of the patients whose MTX regimen was increased to 12.5 mg weekly relapsed again, while our patients received only 10 mg weekly. RA and GCA are both T helper-1-mediated diseases. Yet while interferon-γ (IFN-γ) and interleukin 12 (cytokines that activate macrophages) are elevated in both diseases[5,6], TNF-α, a product of activated macrophages, is elevated only in RA[5,7,8]. MTX reduces TNF-α production by macrophages and T cells, having only a marginal effect on IFN-γ[9,10]. This may account for the lack of effect of MTX in GCA.

Our cases illustrate 2 points: first, care should attend evaluation of systemic inflammation in patients with RA when there is no apparent synovitis, the differential diagnosis of which should include GCA. Second, in our patients, clinical onset of GCA occurred during treatment with MTX, findings that are in agreement with those of Hoffman and Spiera.

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Book Reviews

A Primer on Musculoskeletal Examination
Evelyn D. Sutton. Halifax: Novont Health Publishing Limited, 2004, 75 pages, soft-cover, $29.95 CAN.

This manual outlines the musculoskeletal examination with chapters covering each anatomical region. Each chapter is organized in a similar fashion and outlines general comments, inspection, palpation, range of motion, special tests, and clinical vignettes. The book is concise and well written and provides a logical overview of the musculoskeletal examination. In each chapter the basic clinical examination is clearly and concisely described. The text is well illustrated, with over 100 clinical pictures demonstrating both physical examination maneuvers and common abnormal clinical findings. Throughout the text the author shares her considerable clinical experience. The clinical vignettes at the end of each chapter provide real-life practical patient problems. These are invaluable for students and trainees, providing an opportunity to verify their acquisition and understanding of the material. Primary care providers will no doubt encounter such problems in daily practice.

The book is best suited for medical students, trainees, and practicing clinicians in non-musculoskeletal disciplines. It is enjoyable and easy to read, and will no doubt eliminate the apprehension some trainees experience when learning the musculoskeletal examination. I believe the author has achieved her objective of facilitating more confidence in learners in their technical and interpretive musculoskeletal examination skills. The book is endorsed by the Canadian Rheumatology Association and should be an essential read for all our medical students and postgraduate trainees.

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Occupational Musculoskeletal Disorders
Nortin M. Hadler. Philadelphia: Lippincott, Williams & Wilkins, 2005, 339 pages, $79.95 US.

Modern occupational medicine is broadly polarized into 2 camps when it comes to occupational musculoskeletal disorders. One camp favors psychological and social causes for the disorders, arguing that specific diagnosis is not possible, and that these illnesses do not arise from the course of work and thus are noncompensable. The other side argues that these disorders are caused by sudden or ongoing biomechanical stresses, and specific diagnosis is possible. Since these disorders arise from the course of work, they advocate changing work demands to prevent them and compensation when prevention fails. Prof. Hadler is perhaps the most enlightened champion of the first position. The book's primary argument is that regional symptoms of the musculoskeletal system are a fact of life, not a disease; the person can choose to deal with them on their own, with recourse to medical attention, and thus become a patient, or declare that they were injured at work, and thus become a claimant.

In 3 sections and 13 chapters, this third edition of Hadler's book provides a lucid description of the historical and philosophical roots and the supporting empirical research for the first position. Little is described of supporting empirical research for the other point of view. Individual chapters discuss axial (back and neck) disorders, fibromyalgia, and upper limb, lower limb, and neurovascular syndromes.

This book is required reading for both camps, and in general for those who make occupational musculoskeletal disorders the focus of their research career or medical practice. Those in the first camp will gain insight to the main philosophical tenets of their position. Those in the second camp will realize the depth and breadth of what they are up against.

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Correction

J Rheumatol 2006;33 Supplement 77. B Cell Targeted Therapies: From Theory to Practice. On the Table of Contents, the introduction to the CME program is incorrectly attributed to authors D.A. Isenberg and A. Kavanaugh. We regret the error.