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.**

Extraarticular Rheumatoid Arthritis and Drug-Induced Syndromes: Understanding the Role of Tumor Necrosis Factor Inhibitors

To the Editor:

I read with great interest the article by Jarrett, *et al*[1], on a case series of 8 patients with rheumatoid arthritis (RA) who developed systemic vasculitis after several infusions with infliximab. The authors implicate an etiopathogenetic role for infliximab in the induction of the systemic vasculitis.

Although infliximab seems the most plausible culprit, it is striking that of their 8 patients, 5 also were treated with leflunomide. Since the introduction of leflunomide on the market, several reports have been published making notice of cases of vasculitis, some with a fatal outcome[2,3]. Therefore, considering infliximab here as the one and only agent responsible for the vasculitis cases of Jarrett, *et al* denies a role for leflunomide — or possibly the combination of infliximab and leflunomide — which could have accounted for some of their cases. In this respect, it is relevant for the reader to know whether the authors have continued treatment with leflunomide; only by reading the table is the reader informed about continuation of leflunomide in Patient 8.

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REFERENCES

1. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-α therapy-induced vasculitis: case series. J Rheumatol 2003; 30:2287-91.
2. Bruyn GAW, Griep EN, Korff KJ. Leflunomide for active rheumatoid arthritis [letter]. Lancet 1999; 353:1883.
3. Bruyn GAW, Veenstra RP, Halma C, Grond J. Anti-glomerular basement membrane antibody-associated renal failure in a patient with leflunomide-treated rheumatoid arthritis. Arthritis Rheum 2003; 48:1164-5.

To the Editor:

We read with great interest the article by Jarrett, *et al* on a case series of 8 patients with rheumatoid arthritis (RA) who developed vasculitic lesions while undergoing anti-tumor necrosis factor (TNF) therapy[1]. The authors suggest this could indicate a drug-induced syndrome, and discuss various mechanisms through which anti-TNF agents could cause the development of vasculitis. They emphasize the importance of watchfulness, given the risk of rare but serious adverse events in patients receiving such therapy. While we agree that patients receiving such treatment should be carefully monitored, and all serious events noted, we think some of the conclusions drawn by the authors warrant further discussion.

It is well known that a subset of patients with RA develop severe extraarticular disease manifestations, including vasculitis[2]. We recently reported that patients with progressive early arthritis, marked by early disability, are at increased risk of developing severe extraarticular manifestations[3]. Most patients who receive TNF inhibitors have more severe and progressive disease, and have usually failed a number of other antirheumatic agents. This means that such patients would be expected to have an elevated baseline risk of developing RA-associated vasculitis. Indeed, the first 3 patients reported by Jarrett, *et al* have a clinical history compatible with systemic rheumatoid vasculitis. They all improved after treatment with cyclophosphamide and methylprednisolone, which has been shown to be an appropriate treatment for rheumatoid vasculitis[4]. That infliximab was withheld prior to improvement thus certainly does not prove that the lesions were drug-induced. An alternative interpretation would be that although infliximab had a major effect on synovitis in 2 of the patients, it failed to prevent the development of vasculitis.

Of the remaining 5 patients, the diagnosis of vasculitis is doubtful in 3 cases. One patient developed a rash that is described as pustular, and another had extensive urticaria. No evidence for vasculitis is presented. A third patient had an episode of focal cerebral ischemia, which could be due to vasculitis, but also to a thromboembolic event on the basis of atherosclerotic vascular disease. Although cerebrovascular disease would, generally speaking, be unusual in a 45-year-old man, it has been shown that severe RA with persistently active disease predisposes to cardiovascular events[5]. In any event, the proposed link to infliximab is by no means self-evident. It has recently been shown that the incidence of cardiovascular disease actually tends to be lower in patients treated with anti-TNF therapy than in patients with RA in general[6]. This could reflect a beneficial effect of aggressive antirheumatic treatment on the risk of cardiovascular events in patients with RA.

Rheumatoid vasculitis may improve after anti-TNF therapy. Several case series of refractory rheumatoid vasculitis responding to TNF inhibition have recently been published[7,8]. On the other hand, it has been reported that scleritis may develop in patients with RA whose joint disease was controlled by TNF-blocking agents[9]. As in the first 3 cases reported by Jarrett, *et al*, the development of this severe extraarticular manifestation suggests that successful anti-TNF therapy for synovitis does not exclude the development of disease-associated extraarticular disease.

Leukocytoclastic vasculitis during treatment with infliximab has been reported in a patient with Crohn's disease[10]. This, and the very interesting recurrence of an infliximab-induced cutaneous vasculitic rash in 2 patients rechallenged with etanercept in the case series reported by Jarrett, *et al*, indicates that idiosyncratic vasculitic reactions may result from treatment with agents directed against TNF. Apparently, such reactions seem to be limited to cutaneous lesions. We suggest that so far no evidence has been presented for a direct role of TNF inhibitors in the development of systemic rheumatoid vasculitis with multiorgan involvement.

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REFERENCES

1. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-α therapy-induced vasculitis: case series. J Rheumatol 2003;30:2287-91.
2. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62-7.
3. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 2003;62:722-7.
4. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med 1984;76:377-84.
5. Wallberg-Jonsson S, Johansson H, Öhman M-L, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol 1999;26:2562-71.
6. Jacobsson LTH, Turesson C, Gulfe A, et al. Low incidence of cardiovascular events in rheumatoid arthritis patients treated with TNF-blockers [abstract]. Arthritis Rheum 2003;48 Suppl:S241.
7. 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.
8. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. Ann Rheum Dis 2003;62:587-8.
9. Smith JS, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Care Res 2001;45:252-7.
10. McIlwain L, Carter JD, Bin-Sagheer S, Vasey FB, Nord J. Hypersensitivity vasculitis with leukocytoclastic vasculitis secondary to infliximab. J Clin Gastroenterol 2003;36:411-3.

Dr. Jarrett, *et al* reply

To the Editor:

Dr. Bruyn makes an important point with respect to the cases of vasculitis. There was an overrepresentation of leflunomide partly because we were studying patients who had gone through an escalating protocol that ended with leflunomide.

However, he is right to suggest that a specific role for leflunomide with vasculitis cannot be excluded. In view of this possibility we did stop leflunomide in nearly all cases, and in several cases washed-out with cholestyramine. These details were not included for the sake of brevity. Obviously the induction of this vasculitis may relate to the high prevalence of antinuclear antibodies seen in patients treated with leflunomide and infliximab[1].

Drs. Turesson and Matteson make some very interesting points regarding the development of vasculitis with anti-TNF therapy. We agree that certain of the patients described had severe rheumatoid arthritis (RA) that would have put them at risk of extraarticular manifestations. We also agree that as patients with severe longterm disease they would have failed multiple therapies. However, importantly, despite this long history of severe disease up until the time of anti-TNF therapy, these patients had had no significant extraarticular manifestations. Furthermore, these were dramatic examples of immune reactions. We have a very large catchment population and many thousand RA patients on therapy with severe disease. Despite this, the incidence of acute vasculitis has diminished dramatically, presumably due to more aggressive therapy, cessation of smoking, and other general improvements in health. The patients reported here represent a majority of the patients with recent presentations of vasculitis.

We specifically described Case 1 as rheumatoid vasculitis because of the long duration of disease, male sex, rheumatoid factor positivity, and nodular disease, all of which are significant risk factors for the development of vasculitis, and thus agree with Turesson, *et al* . We also made the point that in this case continuation of anti-TNF therapy may be desirable. We referred to correspondence from the drug company describing this phenomenon and referenced an article in which cutaneous vasculitis improved with alternative therapy. For Cases 2 and 3, anti-TNF improved the synovitis, but vasculitis still developed. Importantly, these cases developed early in the disease, i.e., within 12 months of onset of symptoms. There was a striking correlation between serological changes and development of vasculitis.

In Cases 6 and 7 the diagnosis was made by clinicians experienced in the diagnosis of vasculitis, while in Case 8 the neuroradiologist diagnosed definite vasculitis, and an extensive search for thromboembolic causes was undertaken, with no significant risk factor identified in a previously fit 45-year-old.

In the 2 cases with biopsy-proven leukocytoclastic vasculitis — we agree that one patient appears to be a purely local reaction that reoccurred on rechallenge with a different agent; in the second case the rash was associated with a change in serology with the development of antinuclear factor and perinuclear anticytoplasmic antibodies (although we accept there was no change in PR3), which point to a systemic reaction.

The improvement with cyclophosphamide and methylprednisolone is unhelpful in distinguishing drug-induced from disease-related vasculitis. We also agree that the improvements seen on withholding a drug do not provide evidence for causation.

Overall, the cases presented were of a spectrum from vasculitic rashes to systemic vasculitis. We discussed the potential mechanisms and accepted that we could not ascribe causality to all. However, we were struck by the number of cases associated with anti-TNF therapy, especially against the falling incidence of rheumatoid vasculitis.

The fact that anti-TNF has been proposed as therapy for vasculitis was the major reason for publishing the clinical course of these patients. In support of the drug-induced nature of this disease was the change in autoreactivity with development of autoantibodies compatible with a cause for the vasculitis. We feel it is important that clinicians are aware that a presentation of vasculitis in patients receiving TNF could be drug-induced.

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REFERENCE

1. Bingham SJ, Buch MH, Smith S, Barcelos A, Kerr M, Emery P. Universal induction of auto-immunity in patients with RA treated with infliximab and leflunomide. Arthritis Rheum 2004; (in press).

Hormone Replacement Therapy in Rheumatoid Arthritis

To the Editor:

I read with great interest the article by Forsblad d'Elia, *et al* in the July issue[1]. The authors note that the highest incidence of developing rheumatoid arthritis (RA) coincides with the menopause. Unfortunately, that also constitutes a risk factor for developing coronary artery disease.

Cardiovascular death is considered the leading cause of mortality in patients with RA and is responsible for about half the deaths observed in RA cohorts[2]. Further, the increased incidence of cardiovascular events in patients with RA is independent of traditional risk factors[3]. Corticosteroids prescribed in RA may also increase this risk.

Even though the results presented in this article are interesting, they do not influence clinical management of RA. The authors state that no serious side effects were noted with hormone replacement therapy (HRT), but fail to mention how, when, and with what measures these were ascertained in the Methods section. Using HRT as a supplement to conventional therapy in the management of postmenopausal women with RA, who are already at increased risk of cardiovascular events and malignancy, would be unjustifiable in view of the results of recent trials of HRT use among healthy postmenopausal women[4].

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REFERENCES

1. Forsblad d'Elia H, Larsen A, Mattson L-A, et al. Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. J Rheumatol 2003;30:1456-63.
2. Goodson N. Coronary artery disease and rheumatoid arthritis. Curr Opin Rheumatol 2002;14:115-20.
3. Del Rincon ID, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-45.
4. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogens plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.

Drs. Forsblad d'Elia and Carlsten reply

To the Editor:

We thank Dr. Jolly for the valuable comments about our study, which assessed the effects of hormone replacement therapy (HRT) on the course of rheumatoid arthritis (RA) and bone mineral density (BMD) in postmenopausal women[1]. To summarize, HRT decreased clinical and laboratory signs of disease activity, improved BMD, and indicated a joint protective effect. The patients were examined clinically and had a mammography before entry and yearly thereafter. No serious side effects were recorded in our study with a limited number of participants during the 2 study years. In an investigation designed to evaluate the effect of HRT on cardiovascular events and breast cancer incidence in RA, a larger trial would be needed.

We note our study was conducted and the manuscript was submitted before the Women's Health Initiative study[2] was published. No overall increase in the rate of coronary heart disease (CHD) events was found in the HRT group in the previously published HERS I trial in women with established CHD[3].

We do not think it is possible to generalize the results from studies of healthy postmenopausal women, for instance the women in the WHI trial, to patients with RA, a chronic inflammatory disease, since, as Dr. Jolly writes, the increased incidence of cardiovascular events in patients with RA is independent of traditional risk factors. Instead, the systemic inflammation seems to be of large importance in the development of CHD in RA[4]. In our study, the disease activity was reduced in the HRT group assessed by reduction in erythrocyte sedimentation rate and orosomucoid, and increase in the hemoglobin level. We also found that serum levels of soluble interleukin 6 (IL-6) receptor, an agonist to IL-6, decreased in the HRT group[5]. Also, high disease activity has been shown to be associated with increased risk of developing amyloidosis[6] and with the occurrence of lymphoma in RA[7], emphasizing the importance of reducing the systemic inflammation. Accordingly, one may hypothesize that HRT, through its effects on systemic inflammation, theoretically might have a positive influence on outcomes associated with systemic inflammation in postmenopausal women with RA. This speculation can only be confirmed in larger clinical trials.

HRT, composed of estrogens often in combination with progestogens, influences the endocrine and immune system in a multifaceted way not yet completely understood. Hopefully, selective estrogen receptor modulators with potent antiarthritic and antiinflammatory effects, lacking the side effects associated with conventional HRT, would be developed. In the meantime, we agree with Dr. Jolly that there is a need to be cautious about HRT in view of recent trials[2,8]. We therefore believe that treatment of postmenopausal RA patients with HRT has to be individualized for any given patient.

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REFERENCES

1. Forsblad d'Elia H, Larsen A, Mattsson LA, et al. Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. J Rheumatol 2003;30:1456-63.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
3. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-13.
4. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108:2957-63.
5. Forsblad d'Elia H, Mattsson LA, Ohlsson C, Nordborg E, Carlsten H. Hormone replacement therapy in rheumatoid arthritis is associated with lower serum levels of soluble IL-6 receptor and higher insulin-like growth factor. Arthritis Res Therapy 2003;5:R202-R9.
6. Tiitinen S, Kaarela K, Helin H, Kautiainen H, Isomaki H. Amyloidosis — incidence and early risk factors in patients with rheumatoid arthritis. Scand J Rheumatol 1993;22:158-61.
7. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ 1998;317:180-1.
8. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27.

Origins of Erosive Arthritis

To the Editor:

Rothschild, *et al* have documented a fascinating inverse link between rheumatoid arthritis (RA) and tuberculosis (TB)[1]. Studying the 2 diseases in the Archaic and Early Woodland period of North America, they conclude that TB offers protection against the development of RA. Could they have as readily concluded that RA protects against TB?

Immune resistance to *Mycobacterium tuberculosis* derives primarily from the Th1 arm of the immune system[2]. A Th1-charged system, although predisposing to RA[3], may be expected to deter the tubercle bacillus, a rapid Th1-type cytokine release overwhelming the pathogen before it gains a foothold.

One percent of the world's population has RA[4]. The lack of racial, geo-

graphic, or climatic clustering is consistent with a disease having global survival value. *M. tuberculosis* is global and one of the greatest disease scourges of humans, causing more deaths annually than any other human pathogen[5]. Over 8 million new cases of TB and 2 million deaths occur annually. The vigorous mammalian immune response to antigens associated with the mycobacterium species, a phenomenon long appreciated by the response to Freund's complete adjuvant[2], is evidence of the frantic posturing of mammals toward the mycobacterium. An immune system such as that underlying RA, poised and quickly triggered into a Th1-type of immune response, would offer deterrence. However, the price to pay for such a defense would be an immune system poised for robust Th1-weighted responses not only against the tubercle bacillus but also against innocuous agents or even toward micro-injury and manifesting as inflammatory joint damage, i.e., RA.

In *The Journal* last year is a report from Spain that the risk of TB is increased 4-fold in patients with RA[6]. Although this appears on the surface to be in conflict with the Rothschild report it is, on the contrary, consistent with it. Unlike patients with the rheumatoid diathesis, patients with overt clinical disease are debilitated and are treated with drugs such as corticosteroids that specifically target and diminish the Th1 cytokine release that predisposes to RA and protects against TB.

Although the skew toward a Th1 pattern of cytokine response that predisposes to RA may have had survival value at one time, drugs effective against TB have for the most part eliminated that edge. The door may now be open to the pursuit of creative means of reversing this survival mechanism and thereby RA.

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REFERENCES

1. Rothschild BM, Rothschild C, Helbling M. Unified theory of the origins of erosive arthritis: conditioning as a protective/directing mechanism? J Rheumatol 2003;30:2095-102.
2. Haanen JBAG, de Waal Malefijt R, Res PCM, et al. Selection of a human helper type 1-like T cell subset by mycobacteria. J Exp Med 1991;174:583-92.
3. Miossec P, van den Berg W. Th1/Th2 cytokine balance in arthritis. Arthritis Rheum 1997;40:2105-15.
4. Wolfe AM. The epidemiology of rheumatoid arthritis: A review. I. Surveys. Bull Rheum Dis 1968;19:518-23.
5. World Health Organization. 2001 Global tuberculosis control. WHO Report. WHO/CDS/TB/2001, 287:173, 2001. Geneva: WHO; 2001.
6. Carmona L, Hernandez-Garcia C, Vadillo C, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:1436-9.

Dr. Rothschild replies

To the Editor:

Dr. McGrath's considered analysis of our recent article[1] is very much appreciated. The key to understanding is often predicated upon asking the right question. Delineation of the time course of recognition of rheumatoid arthritis (RA) raised the possibility that it actually originated as a New World disease. Affirmative answer to that question[2] and observation of its North American distribution pattern over time[3] raised the possibility that RA is a vector-derived disease[4]. The geographic dichotomy between distribution of RA and that of tuberculosis in ancient North America[1] suggested that perhaps the wrong question was being asked. Rather than ask what is directly causing RA, perhaps it is more appropriate to ask if tuberculosis acts as a conditioning agent. If RA and spondyloarthropathy are related, perhaps this conditioning agent is the determinant for which disease occurs. Perhaps absence of a tuberculosis-related factor is a necessary condition for occurrence of RA.

McGrath asks if our initial question requires further revision. Could the presence of RA have prevented occurrence of tuberculosis? It is unclear how the presence of RA in a relatively few individuals could alter occurrence of tuberculosis in other members of that population. Alteration of immune response in the affected individual might alter their own susceptibility, but it is unclear to me how this would affect "herd immunity" and therefore population resistance to tuberculosis. Further, there is no epidemiologic evidence that Amerindians (in the RA catchment area) were ever actually exposed to tuberculosis. There is certainly no evidence that they came into contact with infected animals[1].

McGrath notes that this question does not negate our hypothesis, but actually extends it to address a further issue: Is tuberculosis less common among individuals with RA? If so, then does RA have a global survival value? It is intriguing that this question is raised. First, such assessment has been offered for spondyloarthropathy, for which there has been clear demonstration of geologic time longevity[5], panspecific mammalian distribution[6], and geometric increase in frequency over time[7,8]. Second, it requires interpretation of reports, such as that of the EMECAR Study group[9]. McGrath very appropriately points out the confounding effect of contemporary therapeutics, the very reason why study of ancient populations (free of effects of contemporary therapeutics) provides such valuable and otherwise unattainable insights[10]. However, analysis of frequency reports[9] also requires reconsideration of the clinical issue of diagnostic lumping and splitting[11]. Some rheumatologists classify as having RA individuals that others would classify as having spondyloarthropathy. We suggested very specific criteria[11] for classification of individuals with inflammatory arthritis as having RA. They include periarticular osteopenia and marginally (not subchondrally distributed) symmetrical polyarticular erosions, in the absence of axial (odontoid disease excepted) involvement or of peripheral joint fusion. Application of such limiting criteria (to individuals with inflammatory arthritis who develop tuberculosis) will perhaps allow confident clarification of the question — does RA protect the individual from infection with tuberculosis?

The clear recognition that much of our current therapeutics predispose to infection is one of the factors propelling the ongoing effort to uncover new approaches. Progress will likely derive from learning to ask the right question.

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REFERENCES

1. Rothschild BM. Unified theory of origins of erosive arthritis: Conditioning as a protective/directing mechanism? J Rheumatol 2003;30:2095-102.
2. Rothschild BM, Turner KR, DeLuca MA. Symmetrical erosive peripheral polyarthritis in the Late Archaic Period of Alabama. Science 1988;241:1498-501.
3. Rothschild BM, Woods RJ, Rothschild C, Sebes JI. Geographic distribution of rheumatoid arthritis in ancient North America: Implications for pathogenesis. Semin Arthritis Rheum 1992;22:181-7.
4. Rothschild BM. Rheumatoid arthritis at a time of passage. J Rheumatol 2001;28:245-50.
5. Rothschild BM. Origin of spondyloarthropathy in the Jurassic. Lancet 2002;360:1454.
6. Rothschild BM, Rothschild C. Spondyloarthropathy as a trans-mammalian phenomenon, reproducible in its manifestations across species lines. J Paleopathol 2000;11:103-4.
7. Rothschild BM, Prothero DR, Rothschild C. Origins of spondyloarthropathy in Perissodactyla. Clin Exp Rheumatol 2001;19:628-32.
8. Rothschild BM, Rothschild C. Epidemic of spondyloarthropathy in

baboons. J Med Primatol 1996;25:69-70.
9. Carmona L, Hernandez-Garcia C, Vadillo C, et al, EMECAR Study Group. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:1436-9.
10. Rothschild BM, Martin LD. Paleopathology: Disease in the fossil record. London: CRC Press; 1993.
11. Rothschild BM. Two faces of "rheumatoid arthritis": Type A versus type B disease. J Clin Rheumatol 1997;3:334-8.

Comparison Between Ultrasound and Magnetic Resonance Imaging of Achilles Tendon Enthesopathy in Patients with Psoriasis

To the Editor:

We have read with great interest the report by Kamel and coworkers[1] on the diagnostic evaluation of heel enthesitis in patients with seronegative arthropathy. In particular, we found the comparison between ultrasound (US) and magnetic resonance (MR) data very stimulating.

Indeed, in a recent study on Achilles tendinitis in psoriatic subjects[2] we demonstrated in 59 patients and 50 healthy volunteers that US is a safe and reliable method to detect the frequent changes in Achilles tendon and peritendinous tissues that may be associated with the enthesopathic involvement. Based on our experience and on data from the literature[3-7], we are now conducting a new study to identify ever-earlier evidence of enthesopathy in psoriatic subjects with and without arthropathy, and to optimize use of the various imaging techniques to detect relevant signs of disease. US evaluation is being integrated with color Doppler and unenhanced and contrast-enhanced MR examination of Achilles tendon.

We are currently evaluating data from 22 psoriatic patients (17 men and 5 women; age range 19–72 years, mean 48; Psoriasis Area and Severity Index[8] scores between 8.6 and 47.1, mean 14), 16 of whom have been diagnosed with psoriatic arthropathy. Subjects were studied with an Aplio (Toshiba) US machine, using an 8–13 MHz multifrequency linear transducer, equipped with color Doppler to detect possible intra- or peritendinous vascular changes. Patients also underwent MR scanning in a superconducting 0.2 Tesla E-Scan XQ Esaote magnet using a surface coil. T1 and T2 weighted sequences were acquired on axial and sagittal planes, and gradient echo and short-time inversion recovery sequences on the sagittal plane. Axial and sagittal T1 weighted sequences were acquired after administration of a 0.1 mmol/kg bw bolus of dimeglutine gadopentate (Magnevist, Schering, Berlin, Germany).

Preliminary results confirm the sensitivity of US in depicting early signs of Achilles tendon involvement; in particular, intratendinous microcalcifications (the outcome of previous degenerative tendon damage now in reparative evolution) were identified in 6 patients, and signs of bursitis in 6 more. MR was less sensitive, especially regarding identification of microcalcifications (not detected in any patient), whereas the 2 methods yielded similar results in the evaluation of tendon changes (enlargement and degenerative areas) and peritendinous thickening; in 2 patients, however, US allowed detection of degenerative changes measuring less than 3 mm that were not seen with MR.

The contribution of color Doppler does not seem significant; this is not surprising, since vascular changes are typical of acute inflammation, and most of the patients enrolled to date receive an antiinflammatory therapy for their arthropathy, which might mitigate inflammatory changes. Indeed, and interestingly, post-contrast MR images did not significantly improve on unenhanced data.

Our preliminary results confirm the findings of Kamel and coworkers, despite differences in the sample studied. US examination conducted by experienced operators using machines equipped with multifrequency probes — especially high frequencies and thus high spatial resolution — is at present superior to MR in detecting early enthesopathic changes of Achilles tendon, particularly with low-field magnets. US should be considered the imaging technique of choice for early diagnosis, disease evaluation, and followup of psoriatic patients with suspected Achilles tendon enthesopathy.

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REFERENCES

1. Kamel M, Eid H, Mansour R. Ultrasound detection of heel enthesitis: a comparison with magnetic resonance imaging. J Rheumatol 2003;30:774-8.
2. De Simone C, Guerriero C, Giampetruzzi AR, et al. Achilles tendinitis in psoriasis: clinical and sonographic findings. J Am Acad Dermatol 2003;49:217-22.
3. Richards PJ, Dheer AK, McCall IM. Achilles tendon (TA) size and power Doppler ultrasound changes compared to MRI: a preliminary observational study. Clin Radiol 2001;56:843-50.
4. Balint PV, Sturrock RD. Inflamed retrocalcaneal bursa and Achilles tendonitis in psoriatic arthritis demonstrated by ultrasonography. Ann Rheum Dis 2000;59:931-3.
5. Schweitzer ME, Karasick D. MR imaging of disorders of the Achilles tendon. AJR Am J Roentgenol 2000;175:613-25.
6. Movin T, Kristoffersen-Wiberg M, Rolf C, et al. MR imaging in chronic Achilles tendon disorder. Acta Radiol 1998;39:126-32.
7. Shalabi A, Kristoffersen-Wiberg M, Papadogiannakis N, Aspelin P, Movin T. Dynamic contrast-enhanced MR imaging and histopathology in chronic Achilles tendinosis. A longitudinal MR study of 15 patients. Acta Radiol 2002;43:198-206.
8. Frederickssson T, Petterson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978;157:238-44.

Drs. Kamel, *et al* reply

To the Editor:

We thank Dr. De Simone and coworkers for their valuable data and interest in our work[1]. Enthesopathy is an evolving area for applied clinical research. The diagnosis of enthesitis in clinical practice is difficult, and typical conventional radiography was almost not helpful. Too many patients are underdiagnosed and/or misdiagnosed because early pathological changes of enthesis in the different types of spondyloarthropathies are not detected[1-3].

We agree that ultrasound (US) imaging proved to be more sensitive and accurate than other imaging modalities in detecting enthesopathy. US examinations usually show reliable evidence for: loss of fibrillar echo pattern, lack of homogenous pattern with flaring of tendon margins, irregular fusiform tendon thickening, and hyperechoic intratendinous lesions with ill defined focal defects filled with a mixture of fluid, fat, and/or granulation tissue indicating fatty degeneration[1-8]. Further, US shows very early signs of intratendinous calcification that MRI cannot[1-3].

US provides data that help in the diagnosis and identification of different pathological and biomechanical changes in the Achilles tendon[1,3,7,8]. We are currently studying enthesitis at other insertion sites such as the patellar knee tendon[2], greater trochanter, iliac crest, deltoid tendon, elbow epicondyles, manubrium sterni, and collateral ligaments of knees and ankles. We believe these studies will provide interesting data for more accurate diagnosis in patients with different types of spondyloarthropathies, particularly psoriasis, Reiter's disease, ankylosing spondylitis, and ulcerative colitis.

We also believe that color Doppler will be more beneficial in detecting early pathological changes in the synovium rather than in the tendons. We suggest that a multicenter study in collaboration with other colleagues would be beneficial.

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REFERENCES

1. Kamel M, Eid H, Mansour R. Ultrasound detection of heel enthesitis: a comparison with magnetic resonance imaging. J Rheumatol 2003;30:774-8.
2. Kamel M, Eid H, Mansour R. Ultrasound detection of knee patellar enthesitis: A comparison with MRI. Ann Rheum Dis 2004;63:213-4.
3. De Simone C, Guerriero C, Gimapetruzzi AR, et al. Achilles tendonitis in psoriasis: clinical and sonographic findings. J Am Acad Dermatol 2003;49:217-22.
4. Kamel M, Moghazy K, Eid H, Mansour R. Ultrasonographic detection of de Quervain's disease. Ann Rheum Dis 2002;61:1034-5.
5. Kamel M, Kotob H. Ultrasonographic assessment of local steroid injection in Tietze's syndrome. Br J Rheumatol 1997;36:547-50.
6. Grassi W, Fillipucci A, Farina A, Salaffi F, Cervini C. Sonographic imaging of tendons. Arthritis Rheum 2000;43:969-76.
7. Gibbon WW, Cooper JR, Radcliffe GS. Distribution of sonographically detected tendon abnormalities in patients with a clinical diagnosis of chronic Achilles tendinosis. J Clin Ultrasound 2000;28:61-6.
8. Fornage BD, Rifkin Md, Touche D, Segal PM. Sonography of the patellar tendon: preliminary observations. AJR Am J Roentgenol 1984;143:179-82.

Silicone Breast Implants

To the Editor:

In his recent editorial[1], Dr. Vasey and his colleagues made reference to our study of symptom-reporting in women with cosmetic breast implants compared with women with breast reduction surgery[2]. In the editorial, Dr. Vasey, *et al* misunderstood our study population and the study conclusions, as they did in an earlier letter on the same study[3,4]. In the Abstract, Results, and Discussion sections of our earlier report[2], we explicitly state that the study population contained women with both silicone-filled (77%) and saline-filled (23%) implants. Nowhere do we present analyses exclusively for women with ruptured silicone implants, as reported in Table 1 of Dr. Vasey's editorial.

In our study, we did examine whether filler type (silicone or saline) and implant size (larger or smaller than the median of the respective implant type) influenced the associations with the symptoms. Risks were not higher among women with larger silicone implants, and thus more silicone gel, compared with smaller implants, and thus less silicone gel; moreover, women with saline implants had twice the rate of local complications compared with women with silicone implants[5].

Contrary to the implications of Vasey, *et al*, no epidemiologic study has found evidence for a new disease or syndrome related to silicone implants[6,7].

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REFERENCES

1. Vasey FB, Alireza Zarabadi S, Seleznick M, Ricca L. Where there's smoke there's fire: the silicone breast implant controversy continues to flicker: a new disease that needs to be defined [editorial]. J Rheumatol 2003;30:2092-4.
2. Fryzek JP, Signorello LB, Hakelius L, et al. Self-reported symptoms among women after cosmetic breast implants and breast reduction surgery. Plast Reconstr Surg 2001;107:206-13.
3. Vasey FB, Mills CR, Wells AF. Silicone breast implants and fibromyalgia [letter]. Plast Reconstr Surg 2001;108:2165-8.
4. Fryzek JP, McLaughlin JK, Nyren O. Response to "Silicone breast implants and fibromyalgia" [letter]. Plast Reconstr Surg 2001;108:2165-8.
5. Fryzek JP, Signorello LB, Hakelius L, et al. Local complications and subsequent symptom reporting among women with cosmetic breast implants. Plast Reconstr Surg 2001;107:214-21.
6. Holmich LR, Kjøller K, Fryzek JP, et al. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. Plast Reconstr Surg 2003;111:723-32.
7. Kjoller K, Friis S, Mellemkjaer L, et al. Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. Arch Intern Med 2001;161:973-9.

Dr. Vasey replies

To the Editor:

We appreciate the work done by Fryzek and McLaughlin in improving understanding of clinical systemic and local symptoms in women with both saline-filled and silicone gel-filled breast implants[1,2]. They rightly point out that the title of our Table 1[3] should not have included "with rupture." We agree rupture is not required before systemic symptoms develop.

The writers' final note, "no epidemiologic study has found evidence for a new disease," deserves comment. Elsewhere[4] they observe, "It is not possible to conduct a rigorous epidemiological study without first having a validated and reliable definition of the disease under investigation." Our editorial was a plea for a new disease definition that epidemiologists could study. We feel strongly that prevalence of symptom studies show statistically increased prevalence of symptoms in women with silicone breast implants compared with controls, as summarized in our editorial[3].

If the flu were undefined it would not exist in the epidemiological world, but in the real world millions of people have it.

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REFERENCES

1. Fryzek, JP, Signorello LB, Hakelius L, et al. Self-reported symptoms among women after cosmetic breast implants and breast reduction surgery. Plast Reconstr Surg 2001;107:206-13.
2. Fryzek JP, Signorello LB, Hakelius L, et al. Local complications and subsequent symptom reporting among women with cosmetic breast implants. Plast Reconstr Surg 2001;107:214-21.
3. Vasey FB, Alireza Zarabadi S, Seleznick M, Ricca L. Where there's smoke there's fire: the silicone breast implant controversy continues to flicker: a new disease that needs to be defined [editorial]. J Rheumatol 2003;30:2092-4.
4. Fryzek JP, McLaughlin JK, Nyren O. Reply to letter. Plast Reconstr Surg 2001;108:2166-7.

Giant Cell Arteritis in a Patient Taking Etanercept and Methotrexate

To the Editor:

I describe the occurrence of giant cell arteritis (GCA) in an elderly woman with long-standing seropositive rheumatoid arthritis (RA), treated for 2 years with etanercept 25 mg twice weekly and methotrexate 7.5 mg weekly. Since etanercept and infliximab were approved for treatment of RA, there has been one report of noncaseating granulomas in pulmonary parenchyma[1] and vasculitis with increased nodulosis[2], and several reports of reactivation of latent tuberculosis in patients taking infliximab or etanercept[3]. These and other complications of tumor necrosis factor-α (TNF-α) receptor-blocking therapy involving activated endothelial cells and granuloma formation suggest a common mechanism of inflammation in susceptible patients.

In summer 2002, a 79-year-old Caucasian woman with RA presented with left jaw pain, so severe that she would not open her mouth to eat. There was associated ear pain and a sore throat. Evaluation by our dental service showed no lesion. The next week when she came into clinic for her injections, she reported worsening pain over the left temporal area. There was no antecedent trauma, and no history of temporomandibular joint involvement in her disease or previous complaints of pain at this site. Present on examination was a thin-walled, tender left temporal artery, with no erythema. There was no evidence on examination of other systemic vasculitis. A biopsy of the left temporal artery showed GCA (Figure 1). Laboratory studies were remarkable for a rising erythrocyte sedimentation rate, 46 to 86, and negative antinuclear antibodies, and she was hepatitis C antibody negative. No HLA testing was done.

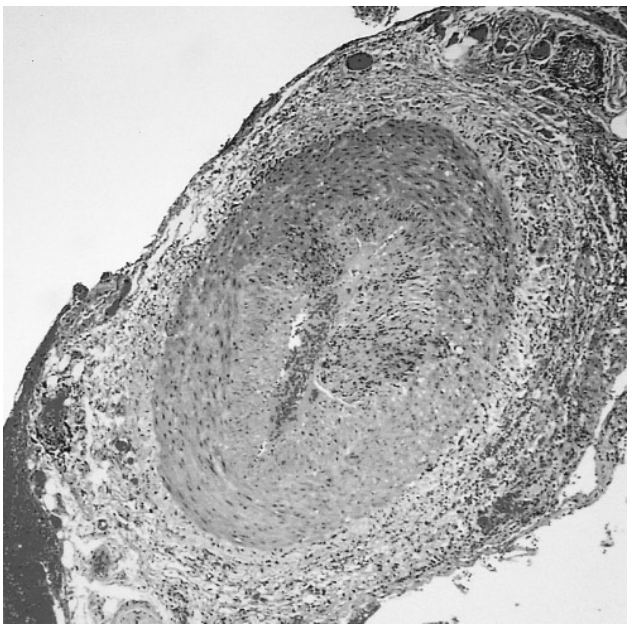

Figure 1. Left temporal artery biopsy revealed GCA in a 79-year-old woman with RA (H & E, ×10).

GCA is commonly reported in association with polymyalgia rheumatica, but it is unusual to see GCA occurring in patients with RA — or at least, it is reported infrequently in the literature. In 1983, 2 groups published cases describing its concurrence, and there has been speculation over the years that RA and GCA may share common pathogenetic mechanisms[4-6]. Studies in GCA have described TNF I (p55) receptor expression in the intima of the large arteries, with immunohistochemical staining revealing TNF-α on endothelial cells, macrophages, and giant cells[7].

Etanercept is a soluble TNF receptor, a fusion protein created from human TNF p75 receptor and the Fc portion of human immunoglobulin G1. Binding to soluble TNF-α, this drug effectively blocks receptor activation in RA, resulting in clinical improvement in many patients. In 2002, Cunnane and colleagues showed images of an inflammatory cell infiltrate in a medium-size arterial wall associated with accelerated nodulosis in patients with RA treated with etanercept[2]. Clinical trials in Crohn's disease suggest etanercept is not effective in Th1 mediated inflammatory bowel disease, although infliximab has some record of success[8]. The reason for this discrepancy is unclear. Clinical studies have been undertaken to examine the efficacy of etanercept in Wegener's granulomatosis. The responses here, too, have been variable, suggesting once again that etanercept may not protect against granulomatous vasculitis[9]. In 2003, Tan, *et al* published a letter describing effective treatment of "resistant" GCA with etanercept in an elderly man with clinical polymyalgia rheumatica and biopsy negative temporal arteritis[10].

The experience with our patient raises the question whether individuals undergoing TNF receptor blockade might be more vulnerable to granulomatous vasculitis, or to other infectious complications requiring effective granuloma formation and intracellular killing. Moreland, *et al* recently reported there is no evident impairment of delayed hypersensitivity reactions in patients taking etanercept, that immunoglobulin concentrations are normal, and there was no excessive risk of infection in the people studied[11]. Clearly, the complications of TNF receptor blockade reported in the literature suggest that at a cellular level, in an aging artery, arteriole, or latent tubercular granuloma, TNF receptor expression and signaling are altered in some way, in some individuals. As clinical trials using anti-TNF agents in granulomatous vasculitis are under way, it is important that clinicians realize that these agents may not be effective in these diseases, and may not protect against them.

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REFERENCES

1. Peno-Green L, Lluberas G, Kingsley T, Brantley S. Lung injury linked to etanercept therapy. Chest 2002;122:1858-60.
2. Cunnane G, Warnock M, Fye KH, Daikh DI. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum 2002;47:445-9.
3. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. New Engl J Med 2001;345:1098-104.
4. Horslev-Petersen K, Helin P. Coexistence of temporal arteritis and rheumatoid arthritis. J Rheumatol 1983;10:831-3.
5. Hall S, Ginsburg WW, Vollertsen RS, Hunder GG. The coexistence of rheumatoid arthritis and giant cell arteritis. J Rheumatol 1983;10:995-7.
6. Salvarani C, Cantini F, Boiardi L, Hunder G. Polymyalgia rheumatica and giant-cell arteritis. New Engl J Med 2002;347:261-71.
7. Cook A, Gallagher G, Field M. Immuno-localisation of tumour necrosis factor and its receptors in temporal arteritis. Rheumatol Int 1997;17:113-8.

8. Podolsky DK. Inflammatory bowel disease. New Engl J Med 2002;347:417-29.
9. Stone J, Uhlfelder M, Hellmann D, Crook S, Bedocs N, Hoffman G. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis Rheum 2001;44:1149-54.
10. Tan AL, Holdsworth J, Pease C, Emery P, McGonagle D. Successful treatment of resistant giant cell arteritis with etanercept [letter]. Ann Rheum Dis 2003;62:373-4.
11. Moreland LW, Bucy RP, Weinblatt ME, Mohler KM, Spencer-Green GT, Chatham WW. Immune function in patients with rheumatoid arthritis treated with etanercept. Clin Immunol 2002;103:13-21.

Is Measurement of Serum Vascular Endothelial Growth Factor Reliable in Patients with Systemic Sclerosis?

To the Editor:

I read with interest the article by Choi, *et al*[1] reporting serum concentrations of vascular endothelial growth factor (VEGF) in patients with systemic sclerosis (SSc). I bring to your attention some methodological concerns that have arisen.

First, serum VEGF levels do not reflect VEGF synthesis by peripheral tissues, and they are not representative of circulating extracellular VEGF level at the time of sampling. In serum, VEGF levels are several-fold higher than in matched plasma samples, owing to *in vitro* release of VEGF from platelets during blood clotting[2,3]. Although various blood cells such as granulocytes, monocytes, mast cells, and lymphocytes have been shown to be capable of producing VEGF, these cells are of little importance for the release of VEGF into the circulation[4-6]. Contradictory results on platelet aggregation in patients with SSc have been reported. *In vitro* studies suggest that platelets from patients with SSc are hyperactive[7,8]; these observations may justify the increased levels of serum VEGF measured by the authors in patients with SSc compared with healthy controls. CTAD (citrate, theophylline, adenosine, dipyridamole) plasma is recommended for the measurement of circulating extracellular VEGF[9].

Second, the authors did not report the condition of processing (i.e., force of centrifugation, time and temperature between blood collection and processing). When VEGF levels are measured, standardization in the collection of serum is relevant and it should be declared. VEGF is released from the platelet in serum in a time-dependent manner. Allowing whole blood sample to clot 2 to 6 hours before serum is collected reduces time-dependent, non-uniform release of VEGF[6]. In addition, centrifuging samples at variable centrifugal forces or for variable times can affect platelet activation by mechanical stress, and consequently may influence VEGF levels. The authors suggest that "high VEGF levels may serve as a surrogate indicator of capillary damage in SSc." In a clinical situation, where blood samples are taken and left for variable times before processing, the contribution from the clotting process would effectively rule out the use of serum measurement. However, even if strict uniformity of clotting time is applied to all samples, the large interpersonal variation in generation of VEGF in clotted samples may invalidate the results[2].

Third, platelet count is significantly correlated to VEGF serum level[6]. When VEGF levels are measured from serum samples, it is advisable to correct the measurement to platelet count[10].

In light of these considerations, I believe the results reported by the authors should be confirmed on plasma samples. The use of plasma samples may improve the value of circulating extracellular VEGF as an indicator of capillary damage in patients with SSc.

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REFERENCES

1. Choi JJ, Min DJ, Cho ML, et al. Elevated vascular endothelial growth factor in systemic sclerosis. J Rheumatol 2003;30:1529-33.
2. Webb NJ, Bottomley MJ, Watson CJ, Brenchley PE. Vascular endothelial growth factor (VEGF) is released from platelets during blood clotting: implications for measurement of circulating VEGF levels in clinical disease. Clin Sci Lond 1998;94:395-404.
3. Gunsilius E, Petzer A, Stockhammer G, et al. Thrombocytes are the major source for soluble vascular endothelial growth factor in peripheral blood. Oncology 2000;58:169-74.
4. Grutzkau A, Kruger-Krasagakes S, Baumeister H, et al. Synthesis, storage, and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of VEGF206. Mol Biol Cell 1998;9:875-84.
5. Harmey JH, Dimitriadis E, Kay E, Redmond HP, Bouchier-Hayes D. Regulation of macrophage production of vascular endothelial growth factor (VEGF) by hypoxia and transforming growth factor beta-1. Ann Surg Oncol 1998;5:271-8.
6. Werther K, Christensen IJ, Nielsen HJ. Determination of vascular endothelial growth factor (VEGF) in circulating blood: significance of VEGF in various leucocytes and platelets. Scand J Clin Lab Invest 2002;62:343-50.
7. Friedhoff LT, Seibold JR, Kim HC, Simester KS. Serotonin induced platelet aggregation in systemic sclerosis. Clin Exp Rheumatol 1984;2:119-23.
8. Goodfield MJ, Orchard MA, Rowell NR. Whole blood platelet aggregation and coagulation factors in patients with systemic sclerosis. Br J Haematol 1993;84:675-80.
9. Wynendaele W, Derua R, Hoylaerts MF, et al. Vascular endothelial growth factor measured in platelet poor plasma allows optimal separation between cancer patients and volunteers: a key to study an angiogenic marker in vivo? Ann Oncol 1999;10:965-71.
10. Hormbrey E, Gillespie P, Turner K, et al. A critical review of vascular endothelial growth factor analysis in peripheral blood: is the current literature meaningful? Clin Exp Metastasis 2002;19:651-63.

Autoantibodies to Bactericidal/Permeability-Increasing Protein and Cathepsin G in Systemic Sclerosis

To the Editor:

In a recent article, Khanna, *et al*[1] suggest that bactericidal/permeability-increasing protein (BPI) and cathepsin G are the major antigenic targets of antineutrophil cytoplasmic antibodies (ANCA) in systemic sclerosis (SSc) or scleroderma. We investigated the prevalence of antibodies to BPI, cathepsin G, myeloperoxidase (MPO), proteinase 3 (PR3), lactoferrin, lysozyme, and elastase using a commercial Combi ELISA kit (Diamedix, Miami, FL, USA). Sera of 20 patients with SSc (7 diffuse form, 13 limited form) were examined. In agreement with the findings of Khanna, *et al*[1], we observed that the prevalences of antibodies to BPI (9/20, 45%) and cathepsin G (11/20, 55%) were higher than those of antibodies to MPO (1/20, 5%), PR3 (4/20, 20%), lactoferrin (4/20, 20%), lysozyme (1/20, 5%), and elastase (2/20, 10%). Similarly, in our sera BPI and cathepsin G antibodies were frequently associated (8/9 and 8/11, respectively).

Recently, performing indirect immunofluorescence (IIF) studies on 115 sera from patients with diffuse (n = 55) and the limited form (n = 60) of SSc we found ANCA positivity in 23 cases (20%)[2,3]. In accord with Khanna, *et al*, the only fluorescent patterns were the atypical (15.6% of cases) and perinuclear (4.3%) stainings, while cytoplasmic fluorescence was never found. However, our IIF results were obtained employing ethanol and formalin-

fixed human neutrophils (Inova Diagnostics, San Diego, CA, USA) as substrate[4], while they used only ethanol-fixed human neutrophils.

When we compared[2,5] the clinical and serological features of cathepsin G, MPO, and PR3 ANCA-positive patients with those of cathepsin G, MPO, and PR3 ANCA-negative patients, we found no correlation. In particular, according to the reports cited[2,5], statistical analysis showed no association between cathepsin G positivity and clinical/serological features nor between MPO positivity and kidney involvement.

We confirm the high prevalence of anti-BPI and cathepsin G antibodies and their frequent association in SSc sera. The significance of their presence and that of other ANCA in scleroderma remains unknown.

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REFERENCES

1. Khanna D, Aggarwal A, Bhakuni DS, Dayal R, Misra R. Bactericidal/permeability increasing protein and cathepsin G are the major antigenic targets of antineutrophil cytoplasmic autoantibodies in systemic sclerosis. J Rheumatol 2003;30:1248-52.
2. Grypiotis P, Ruffatti A, Cozzi F, et al. Prevalence and clinical significance of cathepsin G antibodies in systemic sclerosis [Italian]. Reumatismo 2003;55:256-62.
3. Ruffatti A, Grypiotis P, Todesco S. Antineutrophil cytoplasmic antibodies in patients with systemic sclerosis [reply to letter]. J Rheumatol 2003;30:2079-80.
4. Radice A, Vecchi M, Bianchi MB, Sinico RA. Contribution of immunofluorescence to the identification and characterization of anti-neutrophil cytoplasmic autoantibodies. The role of different fixatives. Clin Exp Rheumatol 2000;18:707-12.
5. Ruffatti A, Sinico RA, Radice A, et al. Autoantibodies to proteinase 3 and myeloperoxidase in systemic sclerosis. J Rheumatol 2002;29:918-23.

Gastrointestinal Disease and Psoriatic Arthritis

To the Editor:

Observations suggest that a relationship exists between gastrointestinal (GI) disease and psoriatic arthritis (PsA). A subgroup of patients with PsA has large joint oligoarthritis that is clinically similar to reactive arthritis and the arthritis associated with inflammatory bowel disease (IBD). In addition, microscopic inflammatory changes in the bowel mucosa of patients with active psoriasis and PsA are common[1,2]. These findings have led to the suggestion that GI disease, as well as skin disease, may act as a portal of entry of causative antigens in PsA[2]. Despite these observations, the background frequency of GI disease in patients with PsA has not been well documented. This issue has growing relevance given that the treatment of PsA increasingly involves the use of disease modifying drugs that may adversely affect the GI system.

We studied the prevalence of GI disease in a group of patients with PsA.

One hundred three unselected patients with PsA were recruited from general rheumatology outpatient clinics in Oxford, UK. Ethical approval was obtained from the Central Oxford Research Ethics Committee. Patients were considered to have PsA if they had seronegative inflammatory arthritis and psoriasis[3]. The clinical characteristics of these patients have been reported[4]. A detailed history was taken for the presence of GI disease including a diagnosis of IBD and irritable bowel syndrome (IBS). Patients were also specifically questioned about symptoms of gluten sensitivity. To further screen for celiac disease, IgA antiendomysial antibodies were tested by direct immunofluorescence in 96 of the patients. The results of antiendomysial antibody testing have been reported[5], and are included here for completeness. HLA-B27 was tested in 98 patients by polymerase chain reaction with sequence-specific primers. Data were analyzed using contingency tables. The frequency of IBD and IBS in the study patients was compared with that of historical UK controls[6,7]. P values are expressed as 2-tailed values.

Four of 103 (3.9%) patients had biopsy-proven IBD, compared with the reported prevalence of IBD in the general UK population of 0.4% ($p < 0.001$). There were 3 patients with ulcerative colitis and one with Crohn's disease. All patients with IBD had psoriatic nail and scalp disease. Three had polyarticular disease and one had oligoarticular disease. One patient had significant axial disease, with sacroiliitis on magnetic resonance imaging (but was HLA-B27 negative). HLA-B27 results were available for 3 patients with IBD; all were HLA-B27 negative.

No patient had GI malignancy or celiac disease. Antiendomysial antibodies were negative in all patients. The prevalence of IBS (18%) was comparable to that of the general population.

The most striking finding was the high prevalence of IBD in our patients with PsA: almost 10-fold greater than the general UK population. While this is not an age or sex matched comparison, we believe these results are clinically meaningful. Sampling bias may also lead to an overestimation of the prevalence of IBD in our PsA population. Importantly, our patients were not recruited from an institution with a specialized gastroenterology unit. Clearly, it is impossible to distinguish with complete certainty between patients with PsA and IBD, and patients with enteropathic arthritis and psoriasis. However, all patients recruited into this study met the Moll and Wright criteria for PsA, and were considered to have typical PsA by their usual rheumatologist as well as by the investigators.

Although an increased risk of IBD in patients with PsA has not been widely reported, studies of patients with IBD have shown a high prevalence of psoriasis, ranging from 5.7% to 11.2%[8,9]. Overall, these data support the hypothesis that common genetic or environmental determinants for IBD, psoriasis, and PsA exist. It is unlikely that HLA-B27 is a clinically significant factor in our patients. Rahman and colleagues have recently reported that the *CARD15 (NOD2)* Crohn's disease susceptibility gene also confers susceptibility to PsA independent of HLA-Cw*0602[10]. It would be interesting to study a larger group of patients with IBD and PsA to determine whether shared genetic factors such as *CARD15* gene variants account for this association.

We wish to raise awareness of the association between PsA and IBD. Our data suggest that clinicians should have a high index of suspicion for IBD in their patients with PsA.

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REFERENCES

1. Scarpa R, Manguso F, D'Arienzo A, et al. Microscopic inflammatory changes in colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. J Rheumatol 2000;27:1241-6.
2. Schatteman L, Mielants H, Veys EM, et al. Gut inflammation in psoriatic arthritis: a prospective ileocolonoscopic study. J Rheumatol 1995;22:680-3.
3. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum

1973;3:55-78.
4. Williamson L, Dockerty JL, Dalbeth N, McNally E, Ostlere S, Wordsworth BP. Clinical assessment of sacroiliitis and HLA-B27 are poor predictors of sacroiliitis diagnosed by magnetic resonance imaging in psoriatic arthritis. Rheumatology Oxford 2004;43:85-8.
5. Dockerty JL, Williamson L, Wordsworth BP. Endomysial antibodies in psoriatic arthritis patients. Rheumatology Oxford 2002;41:1195-6.
6. Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. Aliment Pharmacol Ther 2000;14:1553-9.
7. Kennedy TM, Jones RH, Hungin AP, O'Flanagan H, Kelly P. Irritable bowel syndrome, gastro-oesophageal reflux, and bronchial hyper-responsiveness in the general population. Gut 1998;43:770-4.
8. Yates VM, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. Br J Dermatol 1982;106:323-30.
9. Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol 1990;85:962-3.
10. Rahman P, Bartlett S, Siannis F, et al. CARD15: a pleiotropic autoimmune gene that confers susceptibility to psoriatic arthritis. Am J Hum Genet 2003;73:677-81.