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LETTERS

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Refractory inflammatory heel pain in spondylarthropathy: a significant response to infliximab documented by ultrasound

To the Editor:

Enthesitis is a cardinal feature of spondylarthropathy (SpA) (1). One of the most challenging issues in the treatment of SpA concerns refractory heel pain caused by Achilles enthesopathy, retrocalcaneal bursitis, and plantar fasciitis (2). Early reports suggest that the anti–tumor necrosis factor α monoclonal antibody, infliximab, is very efficacious in patients with severe SpA (3,4). We now report our experience with 2 HLA–B27–positive SpA patients who had refractory erosive calcaneal enthesitis without any other articular or axial symptoms, and who experienced significant remission, documented by ultrasonography, following initiation of treatment with infliximab.

Both patients received a 3-mg/kg infusion of infliximab at weeks 0, 2, and 6, which was well tolerated. Control examinations were subsequently performed at weeks 10 and 14. At each visit, heel pain was measured on a visual analog scale (VAS), clinical and ultrasound examinations were performed by independent examiners, and the serum level of C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were determined. Ultrasound examination was performed with real-time high-resolution equipment (AU5 Harmonic; Esaote, Genova, Italy) using a 13-MHz linear array transducer. Inflammatory activity was evaluated using the power Doppler mode at the following settings: medium flow optimum, low wall filter, dynamic range 50 dB, pulse repetition frequency 750 Hz.

The first patient, a 21-year-old man, presented with a 10-year history of inflammatory right heel pain and a 3-year history of left heel pain, corresponding with radiographically evident erosions of both calcanei. Prior treatments had included nonsteroidal antiinflammatory drugs (NSAIDs), sulfasalazine (SSZ) for 2 years, multiple local injections of corticosteroids, local radiotherapy, and even local surgery, all of which proved unsuccessful. The patient had stopped working as a baker because of the disabling heel pain. The level of pain on a 100-point VAS was 76 for the right heel and 56 for the left heel. Physical examination at baseline revealed bilateral painful and tender heels at the insertion of the Achilles tendon and plantaris fascia. Magnetic resonance imaging showed bilateral edema and erosions of the entheseal portion of the calcaneus, inflammatory aspects of the Achilles tendon and plantaris fascia. Ultrasound examination revealed bilateral hypoechoic thickening of the Achilles tendon at the entheses, with calcific deposits and bone cortex erosion of the calcaneus (Figure 1A). Power Doppler sonography showed increased blood flow from the periosteal bone to the entheses of the Achilles tendon and plantaris fascia, predominantly in the left side (Figure 1A).

Partial clinical improvement was noticeable as early as week 2 after the initiation of infliximab treatment (heel pain [for each heel] scored 33 on a 100-point VAS), and complete clinical remission (heel pain scored 0; negative physical findings) was achieved after the second infusion of infliximab (week 6) and was maintained at the next visits. Ultrasonography performed at weeks 2, 6, 10, and 14 showed a progressive recovery of normal entheseal echostructure and disappearance of periosteal vascularity (Figure 1B). The patient resumed his normal activities and planned to return to work.

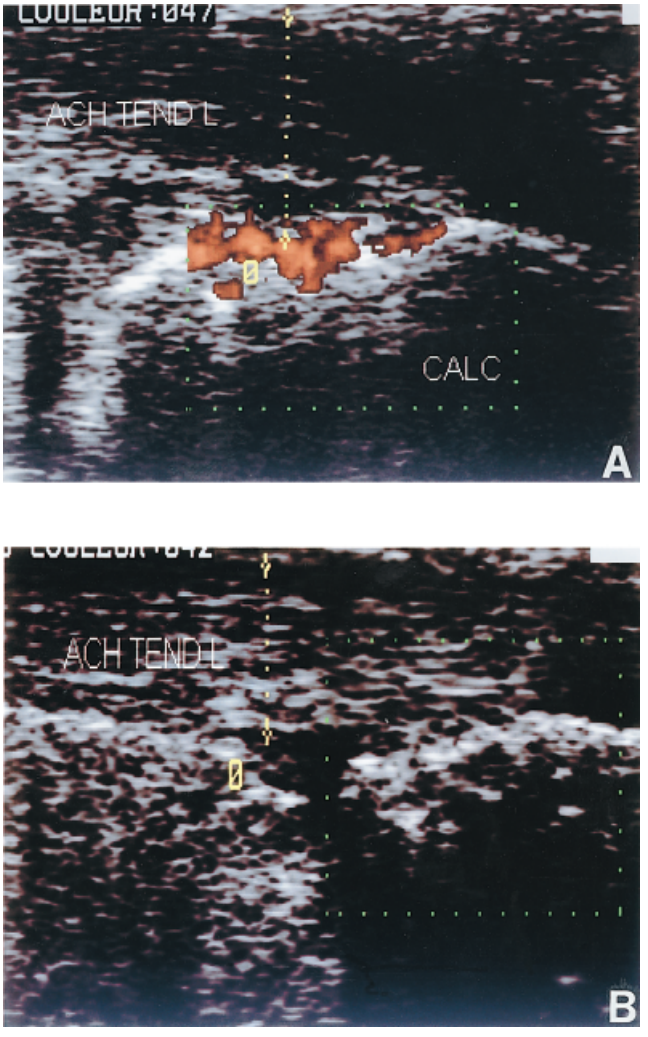

Figure 1. Ultrasonography of left (**L**) calcaneal (**CALC**) enthesitis in a spondylarthropathy patient treated with infliximab. **A**, Baseline. Power Doppler sonography shows hypoechoic thickening of the Achilles tendon (**ACH TEND**) at the entheses, with increased blood flow. **B**, Fourteen weeks after initiation of infliximab treatment. Ultrasonography shows improvement of the echoic pattern of the Achilles tendon and disappearance of periosteal vascularity.

The second male patient, a 17-year-old with SpA, had a 5-year history of disabling left heel pain, a history of previous left hip-joint arthritis, psoriasis, and a family history positive for SpA. Several NSAIDs and SSZ were discontinued because of inefficacy; methotrexate (15 mg/week for 3 months) and 2 local corticosteroid injections had also been ineffective for relieving heel pain. The patient's level of heel pain on a 100-point VAS was 75. Physical examination at baseline revealed pain and tenderness of the left calcaneus at the

insertion of the Achilles tendon and plantaris fascia. Ultrasonography showed an echographic pattern similar to that of the first patient: bilateral hypoechoic thickening of the Achilles tendon at the entheses, calcific deposits, bone cortex erosion of the left calcaneus, and retrocalcaneal bursitis with marked vascularization by power Doppler imaging (not shown). The serum CRP level was 13 mg/liter, and the ESR was 18 mm/hour. The clinical response to infliximab was spectacular, with frank improvement noticeable as early as 2 days after the first infusion. At week 2, heel pain on VAS had decreased to a score of 11, and both the CRP level and the ESR had normalized. All these parameters remained normal during the entire followup period. Ultrasonography at week 14 showed a normal echoic pattern of the Achilles tendons (not shown).

Heel pain is the most frequent extraspinal symptom in SpA (2). It is considered refractory only when it persists for >2 years (2). The remarkable efficacy of infliximab, as reported here, represents a new opportunity to overcome this disabling condition. In addition, ultrasonography coupled with power Doppler imaging appears to be a promising tool for objective assessment of disease activity. Indeed, this method could be an easy-to-handle way to display inflammatory enthesitis and monitor the effect of treatment on extraspinal manifestations of SpA.

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Reply

To the Editor:

We are pleased to comment on the letter by D'Agostino and colleagues, who confirm the international experience regarding the efficacy of anti–tumor necrosis factor (anti-TNF) therapy in SpA. They not only have added 2 more cases to the literature but also have initiated a fruitful discussion about several other issues in this context that must be addressed.

There are several important targets of therapy in SpA: sacroiliitis, spondylitis, arthritis, dactylitis, uveitis, and enthesitis. Enthesitis is especially relevant for 2 reasons. First, although it is not unique to SpA, enthesitis is very characteristic of the disorder (1). Recent imaging data have suggested that the entheses are even more commonly involved in SpA—possibly primarily involved—than was previously thought (2). Second, enthesitis is rare in rheumatoid arthritis (RA), another common inflammatory rheumatic disease, and RA patients respond favorably to anti-TNF therapy. When the pilot study, from this institution, on the efficacy of infliximab in the treatment of spinal inflammation in patients with ankylosing spondylitis (AS) (3) was published, no data on enthesitis were available. Since then, our group has performed a randomized trial in which an enthesitis score was systematically assessed. The data clearly showed that AS patients with enthesitis who were treated with infliximab improved significantly compared with control patients who received NSAIDs only (4).

The 2 SpA cases reported by D'Agostino et al remind us that AS and SpA in general are diseases that clearly have the potential to cause disability in young patients. Both of their patients were younger than age 30 years, and both had to quit their jobs because of chronic heel pain caused by enthesitis. These rather localized disease manifestations were also remarkable for their total duration (5 and 10 years).

Because of the costs of anti-TNF therapy, which are still high, there is a need to discuss such costs in relation to the benefit for individual patients and also for society. In this context, 2 recent studies, by Zink and colleagues and by Boonen et al, have clarified the significant socioeconomic burden associated with AS and should be mentioned (5,6). The efficacy of infliximab therapy in the 2 young patients described by D'Agostino et al suggests that an economic advantage could be associated with early effective antiinflammatory treatment in such patients.

The concept of early treatment prompts consideration of the definition of "refractory" used by D'Agostino and colleagues, based on that proposed by Amor et al several years ago (7). The proposal to call a case "therapy-resistant" after as long as 2 years probably reflects a situation in which no effective treatment was available and, thus, the rheumatologist simply took some time before "giving up." Now, with the availability of effective therapy, we believe that 6 months might be a long enough period in which to try every treatment that is conventionally possible.

Nevertheless, there is a need to more precisely define those SpA patients who qualify for anti-TNF therapy. Clearly, those with severe (2) or refractory (7) disease are the most suitable candidates, but proposals for criteria are awaited. Again, the situation in patients with SpA is different from that in patients with RA, in whom 2 or 3 DMARDs can be tried before anti-TNF therapy is started. Based on our experience, SSZ should be tried first, at least in patients with peripheral arthritis and in those with early active disease. Furthermore, we think that at least 3 NSAIDs and 2 intraarticular steroid injections should be tried before anti-TNF treatment is considered.

The dose (3 mg/kg) used for the 2 patients described by D'Agostino et al differs from the doses used in our study (3) and that by van den Bosch et al (8), in which 5 mg/kg of infliximab was given. Two arguments favor the higher dose. First, a 5-mg/kg dose was found to be efficacious in Crohn's

disease (for which infliximab is approved) and for the joint manifestations of Crohn's disease (9). Crohn's disease seems to be more closely related to SpA than to RA, and 3-mg/kg and 10-mg/kg doses of infliximab have been shown to produce comparable results in patients with rather longstanding RA (10). Second, in a small pilot study of 6 patients with undifferentiated SpA, the 5-mg/kg dose was shown to be more efficacious than the 3-mg/kg dose (11).

Furthermore, the clinical impression that anti-TNF therapy works even better in SpA than in RA has been mentioned by experienced rheumatologists (van der Linden S, Mielants H: personal communication). On the basis of current knowledge, this difference is unlikely to be dose-related. Given that the efficacy of DMARDs and systemic corticosteroids in AS is inferior to that in RA, the question arises as to whether the TNF-antagonizing effect is more critical in SpA than in RA. The data provided by D'Agostino et al could lead to an explanation by showing that infliximab is effective for enthesitis. As mentioned above, the entheses clearly have been found to be more strongly and more frequently involved in SpA than in RA, on the basis of both older histopathologic (12) and more recent magnetic resonance imaging (MRI) studies (1). Thus, the effect of anti-TNF therapy on enthesitis could be critical in SpA, as was shown to be the case in psoriasis (13) and psoriatic arthritis (14).

D'Agostino et al used the power Doppler technique to assess inflammation at the calcaneus, thereby measuring mainly edema and blood flow attributable to neovascularization. This fascinating new technology provides impressive images and has only a slight drawback, which is the subjective influence of the examiner, who has a clear effect on the position of the device and therefore can possibly change the picture significantly. Another imaging technique that has been successfully applied to entheses is MRI (15), which clearly has the capability to effectively monitor followup (16).

Although there is reason to be hopeful about both the acute and lasting effects of anti-TNF therapy in SpA, it must be stressed that long-term experiences to date are limited. Results from our study of a small number of patients suggest both lasting and remitting efficacy of anti-TNF therapy, but we have also observed withdrawals because of side effects (17). Currently, there is no clear indication that the efficacy of infliximab diminishes over time.

Finally, the side effects that have been reported to occur with anti-TNF therapy must be further evaluated. Tuberculosis, lupus-like disease, and allergies have been reported. Although these side effects can be severe, they are treatable and have not been shown to lead to lasting problems for the patients. The overall prevalence of such adverse events does not appear to exceed 5%, and, importantly, the impressive efficacy of this therapy seems to be worth the calculated risk. The risks and benefits of anti-TNF therapy should be discussed with patients.

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Development of rheumatoid nodules during anti–tumor necrosis factor α therapy with etanercept

To the Editor:

Several recent articles in *Arthritis & Rheumatism* have helped extend the use of anti–tumor necrosis factor α (anti-TNFα) therapy to diseases such as chronic uveitis (1) and Wegener's granulomatosis (2) but also have pointed out some previously unknown side effects (3). We now report the new formation of rheumatoid nodules in a 53-year-old woman during anti-TNFα therapy with etanercept. The patient had an 11-year history of rheumatoid factor (RF)–positive, erosive (Larsen IV) rheumatoid arthritis (RA) (4). Treatment with etanercept was initiated after use of different disease-modifying antirheumatic drugs (DMARDs) (initially methotrexate, followed by cyclosporin A and later by azathioprine, all of which were accompanied by at least 5 mg of prednisolone per day) was complicated by side effects and did not result in remission.

We started treating the patient with subcutaneous etanercept (Enbrel, 25 mg twice weekly) while her disease was active (erythrocyte sedimentation rate [ESR] 38 mm/hour, C-reactive protein [CRP] 47 mg/liter, morning stiffness lasting >2 hours). The therapy was well tolerated and resulted in prompt clinical and laboratory improvement (no morning stiffness after 1 week, and a decrease in the CRP level to 15 mg/liter), although the ESR remained unchanged.

The first signs of increased disease activity were noted 3 months later; CRP levels had increased (up to 95 mg/liter), the ESR was 71 mm/hour, and RF titers had increased more than 6-fold. These changes were followed by the reappearance of tender and swollen joints during the next 3 months. Within 4 weeks of the onset of the arthritis symptoms, rheumatoid nodules developed at the patient's elbows and metacarpophalangeal joints. Seven months after the initiation of etanercept therapy, chest radiography and high-resolution computed tomography showed multiple nodules, 1.5 cm in diameter (Figure 1). At that time, the patient reported severe chest pain. Posterior myocardial infarction was diagnosed, and cardiac angiography revealed occlusion of the right carotid artery together with 80% stenosis of the left circumflex artery.

At cardiac surgery, lung biopsy specimens were obtained to allow examination of the pulmonary nodules. Histologic examination showed the typical histomorphology of rheumatoid nodules (Figure 1). Bronchoalveolar lavage and examination of additional stained sections excluded a diagnosis of tuberculosis or lung tumor. Two weeks after surgery (and 6 weeks after discontinuation of etanercept), the patient was taking 10 mg of prednisolone daily and was doing well (ESR 48 mm/hour, CRP 52 mg/liter, no morning stiffness, only swollen wrists). The nodules in both the skin and the lung decreased in size, and leflunomide therapy was started.

Until now, concerns regarding adverse effects of TNFα-neutralizing compounds have focused on infectious complications, malignancies, and the development of autoantibodies (antinuclear antibodies, antineutrophil cytoplasmic antibodies). Rheumatoid nodules are considered to be the most characteristic histopathologic lesion in RA. Previous studies have demonstrated similarities in tissue composition

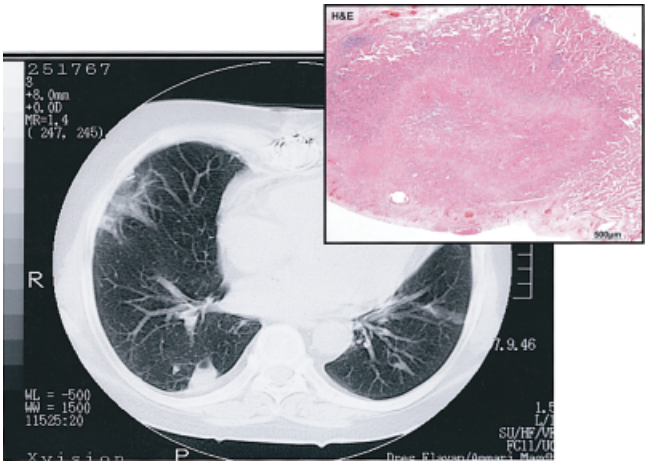

Figure 1. Computed tomography scan of the lung, showing multiple small nodules (up to 1.5 cm in diameter) 7 months after initiation of antirheumatic treatment with etanercept. **Inset,** Histologic examination of hematoxylin and eosin (H&E)–stained lung biopsy specimen, revealing the typical morphology of rheumatoid nodules, with central fibrinoid necrosis and surrounding fibroblastic proliferation.

and the expression of proinflammatory markers (including TNFα) between rheumatoid nodules and inflamed synovium. These observations, together with results of studies of knockout animals, suggest that anti-TNFα treatment inhibits granuloma formation. Of note, TNFα is overexpressed in different granulomas. A study by Seitzer et al revealed a correlation between distinct clinical forms of sarcoidosis (a granuloma-forming disease) and TNFα promoter polymorphisms that may also influence the occurrence of rheumatic nodules in RA (5). Anti-TNFα therapy has also been used successfully in patients with granuloma-forming inflammatory bowel disease.

The present case, in which rheumatoid nodules developed during anti-TNFα treatment, appears to contrast with this picture. It indicates that other cytokines, such as transforming growth factor β (TGFβ) and interleukin-1, may play a pivotal role in granuloma formation and escape control by anti-TNFα therapy. This notion is supported by recent data showing different cytokine patterns in rheumatoid nodules and synovial membranes from the same RA patient (6). Interestingly, recent studies of cytokine expression in RA revealed that anti-TNFα therapy produced no changes in levels of TGFβ (7), which is considered an important factor in the formation of rheumatoid nodules.

This case may also be unique because of the late development of nonresponsiveness to etanercept. The fact that the patient had longstanding RA and was treated with 3 DMARDs without developing rheumatoid nodules or other extraarticular symptoms further raises the question of whether anti-TNFα therapy itself may have contributed to the development of rheumatoid nodules in this patient. It is also interesting that some typical predisposing features for the development of rheumatoid nodules were present, such as positive RF, severe articular disease, and a genetic predisposition as determined by genotyping (HLA–DRB1*04/04 by polymerase chain reaction).

In conclusion, we interpret this case as a delayed nonresponse to anti-TNFα therapy. It must be noted that rheumatoid nodules, even in the lung, can develop during etanercept therapy and must be distinguished from other pulmonary complications of this treatment, such as the relapse of tuberculosis. Our observation may add to the discussion about autoimmune phenomena induced by anti-TNFα therapy and may also provide some early experience of its limited efficacy in systemic rheumatoid diseases such as Still's disease (8).

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Topotecan and the development of scleroderma or a scleroderma-like illness

To the Editor:

We are caring for a patient with ovarian cancer in whom a scleroderma-like illness (clinically identical to idiopathic scleroderma) developed following administration of the chemotherapeutic drug topotecan. The cytotoxicity caused by topotecan is thought to be attributable to its binding to topoisomerase and DNA.

The patient is a 56-year-old woman who underwent a hysterectomy and bilateral oophorectomy following repeated abnormal results of Papanicolaou tests. At the time of surgery, peritoneal washings revealed atypical cells. The level of CA-125 became elevated, and a computed tomography (CT) scan of the pelvis disclosed several enlarged lymph nodes that on biopsy were revealed to be cancer cells of ovarian origin. (Later pathologic review of the ovaries revealed the presence of adenocarcinoma.) Six courses of carboplatin plus taxol were administered, and the CA-125 level returned to normal.

About 1 year later, the CA-125 again reached abnormal levels, and CT scanning revealed enlarged abdominal lymph nodes. Intravenous topotecan, 1.5 mg/m^2, was administered for 5 days per month, starting in May 2000, for a total of 3 months. After the second course of topotecan, the patient's hands became erythematous and inflamed; after the third course, the skin of her hands became tight, and stiffness and erythema increased. Raynaud's phenomenon became apparent, and by August 2000 scleroderma was diagnosed because of slowly progressive generalized skin tightness. The patient had no shortness of breath or dysphagia. Her medical history was negative for major illnesses, and a family history for autoimmune disorders revealed only a distant cousin with rheumatoid arthritis. Physical examination revealed the changes of scleroderma: flexion contractures of the fingers with sclerodactyly, tightness of the face, microstomia, and skin tightness at the arms, chest, abdomen, and feet, with a modified Rodnan skin score of 19. The remainder of the physical examination was normal. Antinuclear antibody testing was positive (titer of 1:640 in a speckled pattern). The patient had no antibodies to SSA, SSB, RNP, Sm, or Scl-70 (topoisomerase I).

Topotecan, an extract from the Chinese tree *Camptotheca acumina,* is approved as a second-line agent for treatment of recurrent ovarian cancer. It binds noncovalently to the DNA–topoisomerase I cleavable complex, interfering with DNA religation and ultimately leading to cell death (1). Its side effects consist mainly of myelosuppression (2). No scleroderma-like illness associated with its use has been reported. Scleroderma-like illnesses have been reported in association with exposure to other chemicals or drugs, especially vinyl chloride, organic solvents, and bleomycin (3). None of these agents specifically affect topoisomerase, although bleomycin may inhibit intracellular DNA replication by damaging the DNA template (4).

Approximately 15–25% of scleroderma patients produce antibodies to topoisomerase I (5). These antibodies are rarely detected in other disorders, although there are some exceptions (6). The role of these antibodies in the pathogenesis of scleroderma is unknown, but recent reports suggest that their binding to topoisomerase may have major significance. In scleroderma patients, titers and immunodominant domains recognized by anti–topoisomerase I antibodies are highly variable (7). Loss of these antibodies can occur over time, conveying a better outcome in scleroderma (8). Topoisomerase may also play an important role in control of collagen gene expression in this disorder (9).

We are aware that the scleroderma-like illness in our patient may be coincidental to use of topotecan. However, the close temporal relationship of the use of topotecan and development of scleroderma suggests a role for topoisomerase

damage in development of scleroderma or a scleroderma-like illness.

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Methotrexate for the treatment of early diffuse scleroderma: comment on the article by Pope et al

To the Editor:

As a long-time advocate of the use of methotrexate (MTX) for diffuse scleroderma (SSc) (Foeldvari I, Lehman TJA. Is methotrexate a new perspective in the treatment of juvenile progressive systemic scleroderma? Arthritis Rheum 1993;36:S218), I was pleased to see the recent report by Pope and colleagues (Pope JE, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum 2001;44:1351–8). However, before accepting their conclusion, "Our findings do not provide evidence that MTX is significantly effective in the treatment of early diffuse SSc," the reader should be aware that this study used what I believe is an inadequate dosage of MTX.

In our 1993 abstract, Dr. Foeldvari and I reported a dramatic improvement in children with SSc who were treated with MTX in a dosage of 1 mg/kg/week (maximum, 50 mg) given either intramuscularly or subcutaneously. I have continued using this regimen for the past 8 years with great success. It is unfortunate that Pope et al chose to use a low dosage of MTX, because I am confident that they would have been able to show a clear benefit if they had used the higher dosage.

The small number of children with SSc hampers pediatric rheumatologists from conducting studies of this type, but our efforts to arrange an appropriate controlled trial of the higher dosage of MTX continue. In the interim, readers should not be dissuaded from using MTX for SSc. The study by Pope et al does not indicate that MTX is ineffective for early SSc but only that the low dose that they used was insufficient to demonstrate a clear effect.

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Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits

To the Editor:

Recently, the frequency of the short genotype of the serotonin transporter (5-HTT) promoter region (5-HTTLPR) polymorphism was found to be higher in a group of fibromyalgia patients than in healthy controls (1). Patients in the short-genotype subgroup exhibited higher mean levels of depression and psychological distress compared with those in the long-genotype subgroup. The 44-bp insertion/deletion has previously been shown to be associated with anxiety-related personality traits (2).

In order to verify and extend these findings, we performed genotyping in a group of 99 female fibromyalgia patients from 2 Israeli ethnic groups. Additionally, we assessed each patient with the Tridimensional Personality Questionnaire (TPQ), a self-report instrument consisting of 100 yes/no questions (3).

A diagnosis of fibromyalgia was assigned according to the currently accepted criteria of the American College of Rheumatology (4). Subjects included 99 female patients with fibromyalgia who were attending the Rheumatology Outpatient Clinic at the Soroka Medical Center. The mean (±SD) age of the patients was 46.3 ± 12.2 years (range 22–70), the mean disease duration was 9.1 ± 8.8 years (range 0.5–52), the mean level of physical functioning was 5.2 ± 6.1 (1–10 scale, 10 = worst), and the mean level of education was 12.1 ± 14.1 years; 68.8% were employed, 89.6% were married, 50.5% were Jewish, and 49.5% were Palestinian Arabs (primarily Bedouin). Exclusion criteria consisted of current or recent substance abuse disorders, psychotic symptoms, and significant cognitive impairment likely to interfere with study procedures or with informed consent. All participants gave written informed consent after receiving a detailed explanation of the purpose and design of the study. Control female subjects were recruited from studies involving normal personalities and were not screened for psychiatric or rheumatic illness. Genotyping

Table 1. Distribution of 5-HTTLPR polymorphism in fibromyalgia patients and controls*

	Genotype				Allele frequency	
	L/L	L/S	S/S	Total	Long	Short
Total population						
Control	150 (26.8)	313 (55.9)	96 (17.2)	559	613 (54.8)	505 (45.2)
Fibromyalgia	34 (34.3)	30 (30.3)	35 (35.4)	99	98 (49.5)	100 (50.5)
Arab population						
Control	12 (22.2)	33 (61.1)	9 (16.7)	54	57 (52.8)	51 (47.2)
Fibromyalgia	14 (29.2)	12 (25.0)	22 (45.8)	48	40 (41.7)	56 (58.3)
Jewish population						
Control	136 (27.4)	275 (55.3)	86 (17.3)	497	547 (55.0)	447 (45.0)
Fibromyalgia	20 (39.2)	18 (35.3)	13 (25.5)	51	58 (56.9)	44 (43.1)

* Values are the number (%).

was carried out as previously described, using standard polymerase chain reaction procedures (5).

The distribution of the 5-HTTLPR genotype in all patients and control subjects is shown in Table 1. The percentage of fibromyalgia patients showing the short/short genotype is twice that observed in the control population (35% versus 17%). The difference in 5-HTTLPR genotype frequencies between the fibromyalgia and control groups was highly significant ($\chi^2 = 25.31$, 2 degrees of freedom [df], $P = 0.00019$). This difference was also significant when each ethnic group was examined separately with its ethnically matched control group (Palestinian Arab, $\chi^2 = 15.10$, $P = 0.001$; Jewish, $\chi^2 = 7.47$, $P = 0.024$). The difference in allele frequency did not reach significance in the whole sample ($P = 0.095$ by Fisher's 1-sided exact test), in the Palestinian Arab sample ($P = 0.074$), or in the Jewish sample ($P = 0.40$). We also compared the frequency of the 5-HTTLPR genotype in 76 unrelated fibromyalgia patients. Again, as observed in the larger sample, a highly significant difference in the frequency of the 5-HTTLPR genotype was observed between fibromyalgia patients and controls ($\chi^2 = 23.38$, $P = 0.00083$).

We next used multivariate analysis to further unravel the complex relationships between personality, diagnosis, polymorphism, and ethnicity in fibromyalgia. Multivariate testing revealed a significant main effect of diagnosis (Hotelling's T^2 F = 22.23, 4 df, $P < 0.0001$) and ethnicity (F = 10.19, 4 df, $P < 0.0001$). The effect of 5-HTTLPR genotype did not quite reach significance at the $P = 0.05$ level (F = 2.025, 4 df, $P = 0.089$). Significant interactions between diagnosis and ethnicity were observed (F = 4.36, 4 df, $P = 0.002$). Between-subjects testing showed a highly significant effect of diagnosis on 3 of the TPQ traits. Scores on the novelty-seeking scale were lower in fibromyalgia patients than in controls (F = 14.46, $P < 0.0001$), whereas harm avoidance (F = 31.89, $P < 0.0001$) and persistence (F = 41.38, $P < 0.0001$) scores were higher. No effect on reward-directed behavior was observed. There was also a significant association between 5-HTTLPR genotype and the TPQ harm avoidance trait (F = 6.21, $P = 0.013$), which is consistent with the initial report by Lesch et al that the short allele of this polymorphism is associated with anxiety-related traits (2).

The fibromyalgia patients we studied were characterized by extremes of temperament dimensions, especially harm avoidance, for which the TPQ scores of Jewish fibromyalgia patients were higher than those of the comparison group by a full standard deviation. These results "make clinical sense," because depression is a common comorbid feature of fibromyalgia (6), and the personality traits of harm avoidance and neuroticism are correlates of clinical depression and anxiety-related disorders.

The first 2 studies that examined the 5-HTTLPR polymorphism in fibromyalgia showed evidence that the short genotype is associated with fibromyalgia. The association between this polymorphism and fibromyalgia has now been observed in 2 independent studies and across 3 ethnic groups, demonstrating the robustness of this association. It appears likely that the relationship between fibromyalgia and the serotonin transporter may be indirect and mediated by anxiety-related traits. Most important, these findings support the idea that a genetic approach to a complex trait such as fibromyalgia will help elucidate the biologic underpinnings of this disease and allow a more rational approach to drug development and treatment paradigms.

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Effect of intraarticular hyaluronate injections in chondrocalcinosis: comment on the article by Martens

To the Editor:

I read with interest the concise communication by Martens (1) concerning use of hylan G-F 20 injections in the treatment of knee osteoarthritis (OA). There is some controversy in the literature about the pertinence of intraarticular hyaluronic acid (HA) injection in patients with radiologic chondrocalcinosis accompanying knee OA (2,3).

In this regard, I would like to report a case involving a 56-year-old man with a 15-year history of bilateral knee OA. The patient had read about the efficacy of HA for the treatment of knee OA and stated that he wanted to try it. At that time, an evaluation for knee OA revealed no knee effusions, noninflammatory synovial fluid (white blood cell count 2–3/mm^3) with calcium pyrophosphate dihydrate crystals, and grade 3 bilateral knee OA with chondrocalcinosis seen radiographically. Acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), and corticosteroid injections provided minimal benefit.

I informed him of the possible effect of intraarticular HA injections in patients with pseudogout, but he elected to receive 2-ml injections of 1% sodium hyaluronate in his left knee, once a week for 5 weeks. After the cycle of therapy, severe pain was reduced, and joint mobility improved. He had not taken NSAIDs or colchicine. After another month, he decided to receive a series of intraarticular HA injections in the right knee, and no effusion has been observed thus far.

I believe that more studies are needed to better define the relationship between intraarticular HA injections and inflammation. Meanwhile, it seems clear that reports of inflammatory reactions, as well as reports of the safety and efficacy of viscosupplementation in knee OA with chondrocalcinosis, are important so that we have accurate information about the morbidity of this treatment, especially as use of HA in the treatment of knee OA increases.

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Reply

To the Editor:

Dr. Romera's comments and case report are appreciated. The author describes a patient with underlying chondrocalcinosis and synovial fluid calcium pyrophosphate dihydrate (CPPD) crystals in whom acute synovitis did not develop after he received 1 series of sodium hyaluronate injections in each knee.

Although development of acute synovitis with associated intracellular and extracellular CPPD crystals after hyaluronic acid injections has been reported (1), many individuals with chondrocalcinosis or even synovial fluid CPPD crystals can successfully receive these injections (2), as Dr. Romera reports here. Clinical trials have demonstrated pain relief in individuals receiving hyaluronic acid injections (3,4), and this therapy now appears in guidelines for the treatment of osteoarthritis, such as those published by the American College of Rheumatology (5).

One intriguing aspect of this therapy is that, in some cases and for unknown reasons, it can trigger strikingly acute synovial inflammation. I agree with Dr. Romera that further studies to determine the relationship between hyaluronic acid injection and acute synovitis would be informative and helpful.

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Inflammatory arthritis and the diagnosis and management of iron deficiency: comment on the article by Bultink et al

To the Editor:

We read with interest the article by Bultink et al reporting that ferritin <50 μg/liter in combination with soluble

transferrin receptor (sTfR) >2.50 mg/liter was 100% sensitive and 97% specific for the detection of iron deficiency in patients with rheumatoid arthritis (RA) (1). The difficulty in distinguishing anemia caused by chronic disease from that due to iron deficiency in patients with inflammatory arthritis has been much discussed. Examination of bone marrow stained with Perls' Prussian blue remains the gold standard, and some authors have advocated use of this procedure in the initial investigation of severe anemia in RA (2). However, bone marrow aspiration is both time-consuming and uncomfortable for patients.

Once a diagnosis of iron deficiency is established, an underlying cause must be sought (3). The main purpose of this search is to exclude life-threatening diseases such as peptic ulcer and gastrointestinal carcinoma. Such investigations are often incomplete (4), however, and even when they are thorough, the cause of anemia may never be established, and management may remain unaltered.

We undertook a review of the laboratory results and case notes of patients with inflammatory arthritis who, over the past 3 years, had undergone bone marrow examination to determine the nature of their anemia. No patient was taking iron, and causes of anemia other than chronic disease and iron deficiency had been excluded. Results of the last studies of hemoglobin (Hgb), mean corpuscular volume (MCV), erythrocyte sedimentation rate, and serum ferritin performed prior to marrow aspiration were recorded. Iron deficiency was diagnosed in cases in which stainable marrow iron was absent.

The Rheumatology Department at King's Mill Centre provides care for ~2,000 patients with inflammatory arthritis. Fourteen of these patients had undergone bone marrow aspiration for the investigation of anemia (12 women, 2 men, median age 64 years, mean Hgb value 9.9 gm/dl). The specificity of serum ferritin (<50 μg/liter) was 100%, but 2 of 4 patients with iron-deficient bone marrow had serum ferritin levels >50 μg/liter (sensitivity 50%). The diagnosis of iron deficiency did not determine treatment in either of the 2 patients with iron-deficiency anemia whose serum ferritin levels were >50 μg/liter.

In the first case, a 34-year-old woman with RA developed intermittent normocytic anemia. Initially, no clinical features suggested a cause for iron deficiency. Poor compliance with disease-modifying antirheumatic drugs had led her to rely on nonsteroidal antiinflammatory drugs (NSAIDs). The onset of indigestion prompted performance of an upper gastrointestinal endoscopy and small bowel biopsy; results from both procedures were normal. No further changes in management were made subsequent to bone marrow aspiration.

The second case involved a man with longstanding RA complicated by Felty's syndrome and prior hemorrhage from a duodenal ulcer in whom normocytic anemia developed during treatment with methotrexate and diclofenac. Because he was experiencing dyspepsia, the latter drug was discontinued and was substituted with a proton pump inhibitor before bone marrow aspiration. He was then hospitalized for septic arthritis, and his anemia subsequently resolved.

A third case illustrates the development of iron deficiency shortly after examination of marrow aspirate revealed normal iron stores. The patient was a 27-year-old woman with psoriatic arthropathy. Analysis of bone marrow aspirate revealed normal iron stores (Hgb 10.3 gm/dl, MCV 78 fl, and serum ferritin 29 μg/liter). Six months later, these values were unchanged, except the level of serum ferritin had fallen to 7 μg/liter, consistent with iron deficiency. No clinical features suggested blood loss or malabsorption.

We conclude that the diagnosis of iron deficiency remains difficult in patients with inflammatory arthritis. Introduction of an estimation of sTfR into routine clinical practice would increase the specificity of criteria based on serum Hgb and ferritin <50 μg/liter but may be helpful in only a small group of patients with ferritin levels in the normal range. We found the gold standard of bone marrow aspiration to be both practical and acceptable. Increasing use of proton pump inhibitors or cyclooxygenase 2–specific antiinflammatory drugs in place of nonselective NSAIDs should reduce the incidence of iron deficiency in these patients and consequently the number of bone marrow examinations needed. Determination of sTfR levels may prove helpful in the continued monitoring of patients in whom anemia of chronic disease has been diagnosed. A definitive diagnosis of iron deficiency does not always lead to changes in treatment, especially in premenopausal women, and a prospective multicenter study would be required to determine the cost–benefit ratio of screening for iron deficiency in this group.

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Reply

To the Editor:

We thank Dr. Neame and colleagues for their comments on our study of ferritin and sTfR measurement in anemic patients with RA. We agree with Dr. Neame et al that

diagnosing iron deficiency in patients with inflammatory rheumatic diseases is difficult. However, the automated measurement of sTfR combined with measurement of serum ferritin proved to be useful for detecting iron deficiency in anemic RA patients in both our study and that of Suominen et al (1). In our study of 40 anemic RA patients, use of a combination of serum ferritin (<50 μg/liter) and sTfR (>2.50 mg/liter) was 100% sensitive and 97% specific for the detection of bone marrow iron deficiency.

We wonder whether Neame and colleagues used the generally accepted scientific meanings of the terms sensitivity and specificity. They describe 4 patients with iron-deficient bone marrow, 2 of whom had serum ferritin levels >50 μg/liter. Using these data, the specificity of their serum ferritin measurement for detecting iron deficiency is not 100% but only 50%, because specificity is defined as the true negative rate (2).

The main issue concerning anemia in RA patients is not how to interpret a low serum ferritin level but how to detect iron deficiency in patients with normal serum ferritin values, because serum ferritin levels may be increased in RA patients due to the acute-phase reaction. This problem is reflected by the observation in our study that a low level of serum ferritin is 100% sensitive for detecting iron deficiency. The specificity of serum ferritin alone was 81%, and specificity increased to 97% when the combined measurement of ferritin and sTfR was used in our patients.

We prefer the results of our cross-sectional study to the data of Neame et al, because we assessed the value of serum markers of iron metabolism, including sTfR, for predicting iron deficiency in a larger and homogeneous group of patients.

The conclusion drawn from our study, which included a considerable number of patients, remains that combined measurement of sTfR and serum ferritin is useful for detecting iron deficiency in anemic RA patients. Additional measurement of sTfR is especially helpful in anemic RA patients whose serum ferritin levels are in the normal range.

Finally, we fully agree with Neame and colleagues that further research is needed to determine the clinical applicability of this method in patients with RA and other inflammatory diseases.

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Absence of anti–cyclic citrullinated peptide antibodies in antineutrophil cytoplasmic antibody–associated vasculitis

To the Editor:

Anti–cyclic citrullinated peptide antibodies (anti-CCP) are autoantibodies specific (96%) for rheumatoid arthritis (RA) (1). The clinical relevance of this antibody was recently underscored by the finding that the presence of anti-CCP in the early stages of RA was associated with more severe radiologic damage after 6 years of followup (2).

Patients with vasculitis involving small vessels often present with migratory arthritis and/or arthralgias. In addition, rheumatoid factor (RF) is detected in many of these patients, and a false diagnosis of seropositive RA is sometimes made (3). We hypothesized that anti-CCP could be a useful diagnostic marker for distinguishing seropositive RA from RF-associated vasculitis. To study this hypothesis, we tested all consecutive serum samples from patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis who were prospectively followed up at the Vasculitis Clinic in Groningen, The Netherlands, starting September 1996 (4) and who proved to be positive for IgM RF (>20 IU/ml), as measured by nephelometry.

Of 133 patients with ANCA-associated vasculitis, 34 (26%) were IgM RF–positive. Of these 34 patients, 28 (82%) had migratory arthralgias and/or arthritis. Fifty IgM RF–positive serum samples were selected (median value 47 IU/ml, range 20–1,210.) Anti-CCP antibodies were detected in 3 samples derived from 3 patients, all of whom were diagnosed as having Wegener's granulomatosis and had presented with migratory arthritis/arthralgias. One of these patients had disease activity limited to the upper and lower airway, whereas the other 2 had generalized disease with respiratory tract and renal involvement. During treatment, complete remission was induced in all 3 patients, and none developed erosive disease during long-term followup (5–13 years after diagnosis).

In conclusion, RA and ANCA-associated vasculitis may be difficult to distinguish in the early phase of disease, especially in patients with vasculitis who are RF-positive. The presence of anti-CCP may be useful for distinguishing RA from ANCA-associated vasculitis, although anti-CCP may occasionally be observed in patients with the latter disease. This study confirms the usefulness of testing for anti-CCP in patients who present with arthralgias and/or arthritis.

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DOI 10.1002/art.10086

Catastrophic antiphospholipid syndrome associated with typhoid fever: comment on the article by Hayem et al

To the Editor:

We read with great interest the article by Hayem et al (Hayem G, Kassis N, Nicaise P, Bouvet P, Andremont A, Labarre C, et al. Systemic lupus erythematosus-associated catastrophic antiphospholipid syndrome occurring after typhoid fever: a possible role of Salmonella lipopolysaccharide in the occurrence of diffuse vasculopathy-coagulopathy. Arthritis Rheum 1999;42:1056–61) suggesting a link between *Salmonella typhi* infection and catastrophic antiphospholipid syndrome (CAPS) in a patient with inactive systemic lupus erythematosus with asymptomatic lupus anticoagulant and high-titer anticardiolipin antibody (aCL).

We now report the case of a young man with typhoid fever in whom CAPS developed, manifesting as a common iliac vein thrombosis. The 42-year-old patient was admitted to the American University of Beirut Medical Center for investigation of a 1-week history of high-grade fever and generalized weakness and fatigue. No other localizing symptoms were reported. The patient appeared ill, and he had a fever of 40°C. Cultures of 3 blood samples taken at the time of admission grew *S typhi* after 3 days of incubation. The patient was treated with intravenous ceftriaxone (2 gm twice daily) for 8 days, followed by oral ciprofloxacin (750 mg twice daily) for 2 weeks.

One month after the onset of typhoid fever (1 week after discontinuation of the antibiotics), he presented with acute swelling and pain in his left lower extremity. He reported no associated fever or chills, and he had been fully ambulatory and well hydrated before the occurrence of these symptoms. On physical examination he was afebrile, and his left lower extremity (up to the inguinal area) was diffusely swollen, hot, and tender.

Duplex scanning of the lower extremities revealed acute deep vein thrombosis in the left common and superficial femoral veins. A computerized tomographic scan of the abdomen and pelvis revealed a filling defect in the inferior vena cava starting at the level of the second and third lumbar vertebrae, extending down to the left common iliac vein and reaching the left femoral vein, with dilatation of these veins. The right iliac and femoral veins appeared normal, and no lymphadenopathy or organomegaly was detected. The prothrombin and activated partial thromboplastin times were normal, as were the levels of fibrinogen, protein C, protein S, antithrombin III, and total serum protein. Other laboratory findings were as follows: no mutation of factor II and factor V (Leiden); negative lupus anticoagulant; IgM aCL, 30 IgM phospholipid units (normal <12.5); and IgG aCL, 25 IgG phospholipid (GPL) units (normal <15).

He received intravenous heparin for 1 week and upon discharge was given oral warfarin (international normalized ratio 2–2.5). Gradual resolution of the swelling and pain in the left lower extremity was noted. One month later, IgM aCL was negative, and IgG aCL was positive (22 GPL units). Two months later, both IgM and IgG aCL were negative.

This case may lend further support for a link between the bacterial antigens of *S typhi* and the induction of CAPS.

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