LETTERS TO THE EDITOR

Does lymphoma 'cure' rheumatoid arthritis?

Prolonged remission in established rheumatoid arthritis (RA) is extremely rare. During a six year follow up of 458 patients Wolfe and Hawley¹ observed two prolonged remissions of more than 48 months, and concluded that 'once established, RA tends to remain, interrupted briefly in a small minority of patients by remission of disease.' However prolonged remissions or cures have been described as secondary to Cushing's disease² and human immunodeficiency virus infection.^{3,4} We have observed a case of cure of RA accompanied by, and probably secondary to the development of γ heavy chain disease in the context of secondary Sjögren's syndrome.⁵

RA was diagnosed in January 1986, in a 53 year old woman. Retrospective examination of her chart shows the presence of six of seven 1987 American Rheumatism Association revised criteria for the diagnosis of RA.⁶ Her treatment included intramuscular gold, non-steroid anti-inflammatory drugs, and several intra-articular injections of corticosteroids. Considerable improvement was noted at the end of 1988 and has persisted since. Gold injections (cumulative dose 2.4 g) were discontinued in March 1989 after discovery of proteinuria. The rheumatoid factor assay peaked at 1/1280 in May 1986 and was negative in April 1989. The sicca syndrome clinically attributed to secondary Sjögren's syndrome, occurred in 1988 and has persisted since with enlargement of the salivary glands and the eyelids. Eyelid 'fat' was removed in August 1995 for cosmetic and functional purposes and showed infiltration by a monotonous population of small lymphocytes. There was decreased γ globulinaemia (4.8 g/l, normal value = 6 to 16 g/l) with free monoclonal γ heavy chains representing 75% of total IgG and an additional faint IgG κ band suggestive of a second monoclonal paraprotein. Flow cytometry of blood and bone marrow confirmed the presence of two B cell clones. The eyelid enlargement recurred quickly. Subsequent irradiation relieved the visual fields obstruction and was later successfully extended to the swollen submandibular regions. Sixteen months after diagnosis, the patient's condition is stable.

The immunologically active polyclonal γ globulin concentration was 1 g/l (reference value 5.4 to 14.8), which is lower than in other leukaemias/lymphomas. The levels of IgA (0.38 g/l, reference value 0.65 to 1.48) and IgM (0.28 g/l, reference value 0.45 to 2.6) were also low. Lymphocyte count was 1120/ μ l with 54% of T cells and most of the B cells part of the clonal processes. Fifteen months later the paraprotein levels were stable, the polyclonal IgG have increased to 3 g/l, IgA to 0.55 g/l, IgM to 0.35 and lymphopenia worsened at 800.

We think that the following chain of events occurred in this case: immune disorder, autoimmune disease (RA and secondary Sjögren's syndrome), malignant B cell

neoplasm, secondary immunodeficiency with cure of the RA. The first three steps are well known, the fourth is probably exceptional but this case and others^{2,3} suggest that secondary immunodeficiency should be considered during spontaneous cures of well established RA.

ALAIN DUMAS

JAMES STRAUCHEN

Department of Pathology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574, USA

- 1 Wolfe F, Hawley DJ. Remission in rheumatoid arthritis. *J Rheumatol* 1985;12:245-52.
- 2 Senécal JL, Uthman I, Beauregard H. Cushing's disease-induced remission of severe rheumatoid arthritis. *Arthritis Rheum* 1994;37:1826.
- 3 Calabrese LH, Wilke WS, Perkins AD, Tubbs RR. Rheumatoid arthritis complicated by infection with the human immunodeficiency virus and the development of Sjögren's syndrome. *Arthritis Rheum* 1989;32:1453-7.
- 4 Bijlsma JWJ, Derksen RWHM, Huber-Bruning O, Borleffs JCC. Does AIDS 'cure' rheumatoid arthritis? (letter). *Ann Rheum Dis* 1988;47:350-1.
- 5 Kassan SS, Thomas TL, Moutsopoulos HM, *et al.* Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978;89:888-92.
- 6 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.

Insufficiency fracture of the sacrum revealing a pregnancy associated osteoporosis. First case report

Osteoporosis of pregnancy, usually responsible for spinal or femoral fracture,¹ is rare as is insufficiency fracture of the sacrum, usually occurring in the elderly.² Magnetic resonance imaging (MRI) permitted during pregnancy, led us to diagnose an insufficiency fracture of the sacrum revealing a pregnancy associated osteoporosis, never previously reported to the best of our knowledge. Rheumatologists need to be aware of this new cause of pelvic pain during pregnancy.

A 29 year old pregnant (seventh month) woman presented with a spontaneous acute claudication in conjunction with a left hyperalgesic buttock pain. Her past medical history showed: low back pain, since the second month of her pregnancy, relieved by rest and paracetamol; smoking (10 packet years) stopped at the sixth month of pregnancy; one spontaneous miscarriage at six months

Figure 1 Magnetic resonance imaging of the pelvis showing on the left part of the sacrum a high signal intensity on T2 weighted sequences.

responsible for an isocoagulant heparin treatment (Calciparine 0.3 ml $\times$ 3 daily) since the first month of her pregnancy, followed by low molecular weight heparin (Fraxiparine 10 000 IU daily) at the fourth month, without any other abnormality in her menstrual history. She did not take part in athletic activities and had no history of pelvic trauma or osteoporosis family history. Physical examination showed an exquisite painful point on the left sacroiliac articulation. Pelvic MRI was performed, showing on the left part of the sacrum a 'no signal intensity' line surrounded by a low signal on T1 weighted sequences and high signal intensity on T2 weighted sequences with an oedematous area, revealing a longitudinal insufficiency fracture (fig 1). Biological markers, summarised in table 1, were within the normal range except a 25 OH vitamin D deficiency and a moderate increase in alkaline phosphatase activity. There was no evidence for any other disease (for example, excess alcohol, systemic lupus erythematosus, malignancy, etc). The pain disappeared with bed rest. Standard x rays performed after delivery showed the fracture of the sacrum, without marked osteopenia; dual energy x ray absorptiometry examination showed: lumbar spine T score: -1.21; femoral neck T score: -2.02.

Insufficiency fracture of the sacrum is a recently described, rarely reported disorder, occurring usually in the elderly.² The main aetiological circumstances include postmenopausal osteoporosis,³ pelvic irradiation,⁴ corticosteroid induced osteoporosis, and primary biliary cirrhosis.⁵

Pregnancy related osteoporosis is rare and its pathogeny is unknown. It is responsible for painful acute events during pregnancy, in conjunction with spontaneous fractures, usually affecting the spine⁶ and sometimes femoral neck,⁷ wrist or clavicle.¹

Table 1 Biological markers

Biological markers	Patient	Normal range for our laboratory
Serum calcaemia	2.46 mmol/l	2.2-2.6
Serum phosphorus	1.07 mmol/l	0.98-1.3
Alkaline phosphatase	140 UI/l	36-120
Prothrombin	70 g/l	65-75
Creatininaemia	91 μ mol/l	45-90
25 OH vitamin D	4 ng/ml	10-35
Parathyroid hormone gla-protein	27 ng/l	10-65
Antiphospholipid antibody	5.70 ng/ml	4-9
Blood count	negative	
CRP	normal	
ESR	5 mg/l	0-10
Thyroid hormone	21 mm/1st h	5-15
	normal	

CRP=C reactive protein, ESR=erythrocyte sedimentation rate.

Our case is original because both the localisation and the aetiology of the fracture are unusual. To the best of our knowledge, no spontaneous fracture of the sacrum during pregnancy had previously been reported in the medical literature. Calcium disorders may occur during pregnancy⁸; this patient's previous bone status was unknown. The increase in alkaline phosphatase activity could be attributed both to a physiological phenomenon of pregnancy and to vitamin D deficiency. In this case the fracture might have occurred in relation with the vitamin D deficiency (possibly in relation with seasonal variation in winter time and bed rest), a mechanical mechanism (fetus weight, as the fracture occurred during the last trimester), and a metabolic mechanism, related to a long term heparin therapy (> 4 months). Heparin may have been a relevant risk factor, because any other risk factor (malignancy, excess alcohol, systemic lupus erythematosus), would have been detected. The heparin osteopenic effect, probably related to a direct effect on osteoclast development and activity, has been demonstrated during pregnancy with dose related calcium homeostasis disorders induced by heparin, although fractures may occur during low dose, short-term prophylaxis.^{9,10}

Sacrum fracture during pregnancy may be an underestimated occurrence, because of the lack of specificity of the symptoms and because x ray imaging is not possible. Magnetic resonance imaging should be considered instead of radiographs during pregnancy when clinical features suggest sacrum fracture.

VÉRONIQUE BREUIL
OLIVIER BROCCQ
LIANA EULLER-ZIEGLER
Rheumatology Department

ANNE GRIMAUD
Radiology Department, l'Archet University,
Nice 06200, France

Correspondence to: L Euler-Ziegler.

- 1 Saraux A, Bourgeois F, Ehrhart A, Baron D, Le Goff P. Pregnancy-associated osteoporosis. Four case-reports. *Rev Rhum Engl Ed* 1993;60:499-503.
- 2 Mathers D, Allen L, Heller A. Insufficiency fractures of the sacrum. *Ann Rheum Dis* 1993;52:621-4.
- 3 Peh WC, Khong PL, Ho WY. Insufficiency fractures of the sacrum and os pubis. *Br J Hosp Med* 1995;54:15-9.
- 4 Peh WC, Khong PL, Sham JS, Ho WY, Yeung HW. Sacral and pubic insufficiency fractures after irradiation of gynaecological malignancies. *Clin Oncol (R Coll Radiol)* 1995;7:117-22.
- 5 Stabler A, Beck R, Bartl R, Schmidt D, Reiser M. Vacuum phenomena in insufficiency fractures of the sacrum. *Skeletal Radiol* 1995;24:31-5.
- 6 Blanch J, Pacifici R, Chines A. Pregnancy-associated osteoporosis: report of two cases with long term bone density follow-up. *Br J Rheumatol* 1994;33:269-72.
- 7 Fingerhuth RJ. Successful operative treatment of displaced subcapital fracture of the hip in transient osteoporosis of pregnancy. A case report and review of the literature. *J Bone Joint Surg Am* 1995;77:127-31.
- 8 Kohlmeier L, Marcus R. Calcium disorders of pregnancy. *Endocrinol Metab Clin North Am* 1995;24:15-39.
- 9 Barbour LA, Kick SD, Steiner JF, Lo Verde ME, Heddleston LN, Lear JL, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol* 1994;170:862-9.
- 10 Dahlman T. Osteoporotic fractures and recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. *Am J Obstet Gynecol* 1993;168:1265-70.

No endotoxin detected in plasma of patients with ankylosing spondylitis

Endotoxin has long been known to be an important virulence factor for Gram negative bacteria. It is chemically classified as lipopolysaccharide (LPS) and it is one of the major constituents of the outer membrane of Gram negative bacteria. This molecule is also known to be responsible for many injurious effects of Gram negative bacterial infections and thus is clinically important.¹

The pathogenesis of ankylosing spondylitis (AS) is still unknown. A microbial aetiology has been suggested, as increased faecal carriage of *Klebsiella* spp, as well as increased antibody values, particularly against the LPS part of *K pneumoniae* have been reported in AS patients.^{2,3} Furthermore, Wagener *et al*⁴ have reported that the plasma endotoxin concentrations were increased in approximately 30% of the AS patients and that a significant correlation was found between the increased endotoxin values and increased C reactive protein (CRP) concentrations. Therefore, it seems that LPS plays an important part in the pathogenesis of AS.

In this study we have examined the plasma of 28 hospital AS patients (eight females, 20 males; mean age 43 years (range 26-62)); mean erythrocyte sedimentation rate 22 mm/1st h (range 5-64) and the mean CRP value 12 mg/l (range 0-37) from the Rheumatism Foundation Hospital, Heinola, Finland for the presence of endotoxin. The mean (SD) duration of the disease was 14.5 (9.0) years: less than five years for three patients, 5-10 years for nine patients, and more than 10 years for 16 patients.

Blood samples were taken by the Vacutainer blood collection system (Becton & Dickinson Diagnostic Instrument System, Towson, MD, USA) into Vacutainer tubes containing sodium citrate and kept in melting ice until separation of plasma. The samples were centrifuged immediately at 400 g for 10 minutes at +4°C, and plasma carefully removed and stored at -70°C until assayed. All equipment was free of endotoxin.

The concentration of endotoxin in plasma was determined by a chromogenic Limulus assay using Coatest kit (Chromogenix AB, Mölndal, Sweden) with a microtitre modification.^{5,6} The detection limit was 5 pg/ml; among normal controls, endotoxin values do not exceed this concentration.

None of the AS patients had plasma endotoxin concentrations exceeding the level of 5 pg/ml. This is surprising, as increased gut permeability has been found in AS patients⁷ and consequently gut microbes might easily pass through the mucosa to enter the circulation. The increased serum antibody concentrations against LPS of certain enterobacteria in AS patients support this scenario.³ Endotoxaemia may be rapidly transitory, however. Endotoxin could leave the circulation at sites of inflammation, for example, the joints of these patients, as in another HLA B27 associated disease, reactive arthritis.^{8,9} Consequently, it may be that endotoxin is found in circulation only at certain stages of the disease; for instance, Wagener *et al*⁴ showed a clear correlation between increased endotoxin and CRP values in AS patients. Endotoxin may also be bound to the specific endotoxin binding protein¹⁰ and is therefore not detected by the Limulus test.

However, the same assay was used by Wagener *et al*,⁴ who found increased plasma endotoxin concentrations in one third of the AS patients and in up to half of the patients with sacroiliitis and peripheral arthritis or rheumatoid arthritis. In their study the blood sampling and handling was not reported. The Limulus assay is known to be extremely sensitive to contaminants.

In conclusion, in this study we could not confirm the reported findings on increased plasma endotoxin concentrations in patients with AS. However, this does not exclude the concept that endotoxin or LPS may play an important part in the pathogenesis of AS.

O MÄKI-IKOLA
J MERTSOLA
K GRANFORS
National Public Health Institute,
Turku, Finland

P KUUSELA
The Haartman Institute,
Department of Bacteriology and Immunology,
University of Helsinki,
Helsinki, Finland

K LEHTINEN
R VON ESSEN
Rheumatism Foundation Hospital,
Heinola, Finland

H SAXEN
Children's Hospital, University of Helsinki,
Helsinki, Finland

Correspondence to: Dr O Mäki-Ikola, National Public Health Institute, Department in Turku, Kiinamyllynkatu 13, FIN-20520 Turku, Finland.

- 1 Brade H, Brade L, Schade U, Zähringer U, Holst O, Kuhn H-M, et al. Structure, endotoxicity, immunogenicity and antigenicity of bacterial lipopolysaccharides (endotoxins, O-antigens). In: Levin J, Büller HR, Cate J W, Van Deventer S J H, Sturk A, eds. Bacterial endotoxins: pathophysiological effects, clinical significance, and pharmacological control. *Progr Clin Biol Res* 1988;272:17. New York: A R Liss.
- 2 Ebringer A. Ankylosing spondylitis is caused by *Klebsiella*. *Rheum Dis Clin North Am* 1992;18:105-21.
- 3 Mäki-Ikola O, Lehtinen K, Nissilä M, Granfors K. IgM, IgA and IgG class serum antibodies against *Klebsiella pneumoniae* and *Escherichia coli* lipopolysaccharides in patients with ankylosing spondylitis. *Br J Rheumatol* 1994;33:1025-9.
- 4 Wagener P, Busch J, Hammer M, Brunkhorst R. Endotoxin in the plasma of patients with inflammatory rheumatic diseases. *Scand J Rheumatol* 1988;17:301-3.
- 5 Mertsola J, Cope LD, Munford RS, McCracken GH Jr, Hansen EJ. Detection of experimental Haemophilus influenzae type b bacteremia and endotoxemia by means of an immunolimus assay. *J Infect Dis* 1991;164:353-8.
- 6 Levin J, Bang FB. The role of endotoxin in the extracellular coagulation of Limulus blood. *Bull Johns Hopkins Hosp* 1964;115:265-74.
- 7 Smith MD, Gibson RA, Brooks PM. Abnormal bowel permeability in ankylosing spondylitis and rheumatoid arthritis. *J Rheumatol* 1985;12:299-305.
- 8 Mäki-Ikola O, Granfors K. Salmonella-triggered reactive arthritis. *Lancet* 1992;339:1096-8.
- 9 Granfors K, Jalkanen S, Lindberg AA, Mäki-Ikola O, von Essen R, Lahesmaa-Rantala R, et al. Salmonella lipopolysaccharide in synovial cells from patients with reactive arthritis. *Lancet* 1990;335:685-8.
- 10 Heumann D, Bas S, Gallay P, Le Roy D, Barras C, Mensi N, et al. Lipopolysaccharide binding protein as a marker of inflammation in synovial fluid of patients with arthritis: correlation with interleukin 6 and C-reactive protein. *J Rheumatol* 1995;22:1224-9.

MATTERS ARISING

Treatment with etidronate for men with idiopathic osteoporosis

In a recent overview of current and potential future drug treatments for osteoporosis, the therapies for osteoporosis in men were discussed briefly.¹ Osteoporosis in men is a heterogeneous disease of which 50% of the cases are classified as idiopathic osteoporosis (IOP).² Long term data on treatment of men with IOP are not yet available.

In an uncontrolled open study of 22 white men with IOP, we have studied prospectively, the effect of a two year treatment with cyclic etidronate (400 mg/d during two weeks every three months) and calcium (500 mg/d during 10 weeks every three months). All patients were extensively screened to exclude any causes of secondary osteoporosis, such as hypogonadism and hypercalciuria, or any other risk factors. Liver function tests were normal in all patients and there was no excessive alcohol consumption either. Bone mineral density (BMD) measurements were performed every six months in the lumbar spine (L2-L4) and in the femoral neck, using dual energy x ray absorptiometry. Precision was <1% in the spine and <2% in the femoral neck. Results are expressed as mean (SEM). Per cent changes from baseline were analysed by a paired *t* test. Patients with vertebral fractures or a T score of < -2 in the lumbar spine, or both were included (a T score of 1 being the number of standard deviations from the mean bone density of young healthy controls). Mean (SD) age of the patients was 56 (2) years. Seventeen

patients showed fractures of vertebrae (one fracture in seven patients and ≥ two in 10 patients) and 11 patients of the appendicular skeleton (one fracture in eight patients and ≥ two in three patients).

Mean T score was -3.2 (0.3) (range -5.4 to -0.6) in the spine and -2.8 (0.2) (range -5.0 to -0.5) in the femoral neck. After two years of treatment with cyclic etidronate, intention to treat analysis indicated an increase in BMD of +7.3 (1.1)% in the spine (*p*<0.001) and of +2.4 (1.2)% in the hip (*p*<0.05) (fig 1). The increase of BMD in the spine was similar if patients with spinal fractures (n=8) were excluded (+7.9 (2.0), *p*<0.01).

The significant increase of BMD in the spine during cyclic etidronate therapy is comparable to the treatment effect in postmenopausal osteoporosis.³ This is the first study to indicate that cyclic etidronate can significantly increase BMD in the hip of men with IOP and substantial bone loss.

This study suggests that cyclic etidronate may be valuable in men with IOP, although double blind controlled prospective studies, with long term follow up are necessary to adequately assess this. In addition, whether cyclic etidronate will beneficially influence fracture rates in men will probably remain unknown, as large groups of patients are required to study this effect and as osteoporosis is less frequent in men than in women.

PIET GEUSENS
JOHAN VANHOOF
JEF RAUS

Dr L Willems-Instituut, Limburgs Universitair
Centrum, B-3590 Diepenbeek, Belgium

JAN DEQUEKER
JOS NIJS
JO JOLY

Arthritis and Metabolic Bone Disease Research
Unit, K U Leuven, Belgium

Correspondence to: Dr P Geusens.

- 1 Patel S. Current and potential future drug treatments for osteoporosis. *Ann Rheum Dis* 1996; 55:700-4.
- 2 Seeman E, Melton LJ, O'Fallon WM, Riggs BL. Risk factors for osteoporosis in men. *Am J Med* 1983;75:977-83.
- 3 Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-72.

Finger drop in a patient with rheumatoid arthritis

I wish to comment on the case report by McDonald and Smith.¹ Although the authors report that a tomographic arthrograph showed no cystic extension of the joint capsule, the two figures are almost identical

with those previously seen in antecubital cysts in rheumatoid arthritis.² These 'cysts' are corollaries to the popliteal cysts and are generally missed in physical examinations because the bulge they produce often disappears into the fleshy part of the forearm. Clearly, they represent an escape for the effusion in a joint distended by severe synovitis and its products. The proximity of major nerves puts them at risk, as the paper by McDonald and Smith shows.

GEORGE E EHRLICH
One Independence Place -1101
241 South Sixth Street
Philadelphia, Pennsylvania 19106-3731, USA

- 1 McDonald SP, Smith MD. An uncommon cause of finger drop in a patient with rheumatoid arthritis. *Ann Rheum Dis* 1996;55:728-30.
- 2 Ehrlich GE, Guttman G. Valvular mechanisms in antecubital cysts of rheumatoid arthritis. *Arthritis Rheum* 1973;16:259-64.

Authors' reply

We thank Dr Ehrlich for his interest in our case report of a patient with a posterior interosseous nerve lesion, secondary to rheumatoid arthritis with synovitis of the elbow joint.¹ We were not aware of his paper² describing antecubital cysts in rheumatoid arthritis but, as our case was mainly an illustration of an unusual compressive neuropathy rather than a description of synovial cysts of the elbow joint, we would not have included the topic of his paper in our literature search. We agree that there is a similarity between the arthrograms in Dr Ehrlich's paper and that illustrated in our paper. Our case reinforces the conclusions of Dr Ehrlich's paper 23 years ago that antecubital cysts are relatively common, are frequently overlooked, and should be actively sought when a patient with rheumatoid arthritis presents with symptoms suggestive of a compressive neuropathy in the forearm. We hope that our case report and Dr Ehrlich's letter will remind rheumatologists to consider this potentially treatable cause of upper limb disability in patients with rheumatoid arthritis.

M D SMITH
S P MCDONALD
Department of Medicine,
Flinders Medical Centre,
South Road, Bedford Park,
South Australia 5042

- 1 McDonald SP, Smith MD. An uncommon cause of finger drop in a patient with rheumatoid arthritis. *Ann Rheum Dis* 1996;55:728-30.
- 2 Ehrlich GE, Guttman GG. Valvular mechanisms in antecubital cysts of rheumatoid arthritis. *Arthritis Rheum* 1973;16:259-64.

Figure 1 Changes in bone density in the lumbar spine and femoral neck. The number of patients at each time point are shown. **p*<0.05, ****p*<0.001 versus baseline.