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 Hawley[1] 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 disease[2] 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/μl 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.

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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

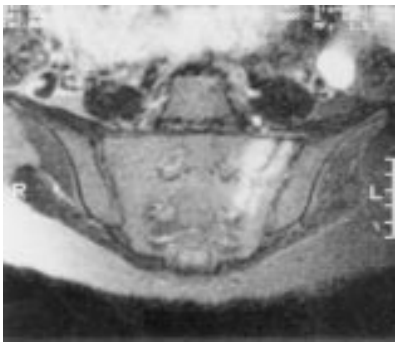

Figure 1 Magnetic resonance imaging of the pelvis showing on the left part of the sacrum a high signal intensity on T2 weighted sequences.

responsible for an isocoagulant heparin treatment (Calciparine 0.3 ml × 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 Tscore: −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 spine[6] 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
Protidemia	70 g/l	65-75
Creatininaemia	91 μmol/l	45-90
25 OH vitamin D	4 ng/ml	10-35
Parathyroid hormone	27 ng/l	10-65
gla-protein	5.70 ng/ml	4-9
Antiphospholipid antibody	negative	
Blood count	normal	
CRP	5 mg/l	0-10
ESR	21 mm/1st h	5-15
Thyroid hormone	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 pregnancy[8]; 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.

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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, particularily 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 patients[7] 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 protein[10] 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.

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