MATTERS ARISING

How should we manage fibromyalgia?

We read with interest your leader, “How should we manage fibromyalgia?”1 We were puzzled by Paul Reilly’s statement that a comprehensive pain management programme has the best chances of success, although even rheumatologists can practise amateur cognitive behavioural therapy in the clinic2. Is Dr Reilly really suggesting that a rheumatologist with amateur efforts at the best outcome for people with fibromyalgia? Dr Reilly offers no evidence to support this statement. He does, however, find evidence to raise questions as to the value of patient self help groups. Dr Reilly cites a 1992 paper that reports an association between membership of such a group and worse prognosis in chronic fatigue syndrome.3 As the authors emphasised the caution with which the results should be interpreted, it is surprising that Dr Reilly has used this evidence to inform his clinical practice.

Firstly, this is ancient research. Things have moved on. Although we would agree that some so called self help groups can end up as a circular review of symptoms, self management courses, which we at Arthritis Care espouse, are a very different matter.

Challenging Arthritis is a self management programme— and that title was chosen very deliberately. It is run by people with arthritis for people with arthritis. It gives people the skills to take control of their lives and their arthritis. It is practical and positive, and it works. The effectiveness of similar programmes in the USA is well recorded.4 Experience in the United Kingdom shows similar results, including better understanding of symptoms, improved communication with medical staff, and increased use of exercise and relaxation techniques. Probably most importantly of all, self management programmes significantly decrease pain, fatigue, and anxiety.5

So it is extremely important to differentiate between navel gazing self help systems and courses such as ours, which encourage people to take control for themselves—and which work.

Similar courses run on the Challenging Arthritis model are now available to people with other chronic conditions.

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t everyone be a welcome adjunct to the United Kingdom. As cognitive behaviour therapy sets out to influence the manner in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self management programme run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education programme can help people with fibromyalgia cope more effectively with their symptoms. However, self help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectives of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” programme is so good and so effective.

Finally, to accuse a paper published in 1992 of being “ancient research” is not only insulting to the authors but also inaccurate. High quality research has a longer shelf life than eight years.

P A REILLY
Frimley Park Hospital, Portsmouth Road, Frimley, Camberley, Surrey GU16 5UF, UK

Author’s reply

I am surprised that Ms Lloyd has chosen to be rather negative about an editorial that was designed to combine optimism with realism. Although one might be optimistic that every patient with fibromyalgia, and similar functional pain syndromes, might have access to professional psychological advice and management, reality dictates that this is not the case, at least not within the health service as it operates in the United Kingdom. As cognitive behaviour therapy sets out to influence the manner in which patients with fibromyalgia think and behave in an attempt to decrease the impact of their disorder, I have merely pointed out that an interested rheumatologist can employ communication and motivational skills, which in many cases will serve the same purpose as formal psychological management.

Ms Lloyd makes much of the “Challenging Arthritis” self management programme run by Arthritis Care. Fibromyalgia, of course, is not a form of arthritis but a form of non-articular rheumatism. I have little doubt that an appropriately run education programme can help people with fibromyalgia cope more effectively with their symptoms. However, self help groups often work to a different agenda than treating clinicians. They function as a lobby to increase recognition and acceptance of a particular disorder, and sometimes such a campaign has financial rewards through litigation and compensation. Not only the objectives but also the objectives of such a group can be called into question. However, I am delighted to learn from Ms Lloyd that the “Challenging Arthritis” programme is so good and so effective.

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P A REILLY
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LETTERS

A “missed” cryoglobulin: the importance of in vitro calcium concentration

Cryoglobulins are immunoglobulins which precipitate at reduced temperature and that redissolve by warming the serum sample to 37°C. Mixed cryoglobulinemia may manifest itself clinically as skin, articular, renal, and peripheral nerve complications.1 To ensure optimal detection, samples must be obtained and preserved at 37°C. We report on a patient whose clinical presentation was suggestive of cryoglobulinemia. Because cryoglobulins had been either undetectable or found at very low levels several years despite repeated careful blood sample examinations with conventional assays, we initially thought he had Henoch-Schönlein purpura. The recent use of a modified assay finally led us to diagnose mixed cryoglobulinemia. Included below is a description of the method used for cryoglobulin detection, emphasising the importance of in vitro calcium concentrations.

Case report

A 52 year old man with multiple lipoma had a 20 year history of polyarthralgies affecting elbows, wrists, hands, knees, and feet, a 10 year history of Raynaud’s disease affecting the hands and feet, and a seven year history of palpable purpura of the lower extremity and chronic fatigue syndrome. In June 1996 he developed attacks of abdominal pain concomitantly with arthralgies and palpable purpura of both legs. Serum creatinine was 95 µmol/l. Gamma-globulins were low (4.2 g/l) on serum protein electrophoresis. Serum concentrations of immunoglobulins were 4.49 g/l for IgG (normal range 6.42–11.92), 1.84 g/l for IgM (normal range 0.52–1.47), and 2.51 g/l for IgA (normal range 1.05–2.85). Other immune rheumatoid factors, including the Rose-Waaler test (Sanoft Pasteur, Marnes La Coquette, France), were positive (table 1), but other serum autoantibodies remaining negative, including antinuclear, anti-DNA, and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C4 <0.06 g/l (normal range 0.10–0.40) and C3c and C3PA (normal range 0.60–1.10) and <0.04 g/l (normal range 0.10–0.40). A complete set of serology markers was negative with tests for hepatitis B and C viruses. Cryoglobulin measurements were initially negative or inconclusive (table 1). Proteinuria was negative. Radiographs of the affected joints were normal. A computed tomographic scan of the abdomen showed a thickened aspect of the duodenal and jejunal loop wall. Skin biopsy was not performed. Prednisone treatment (30 mg/day) was started but, owing to poor response, plasmapheresis was carried out in March 1997; azathioprine (150 mg/day) and colchicine (2 mg/day) were then added and, finally, a marked clinical improvement was obtained. A new flare up occurred in August 1998, again with symptoms including 3 g daily proteinuria of recent onset. The urinary sediment contained 20 red cells per high power field. Renal biopsy showed endocapillary proliferative glomerulonephritis with glomerular crescents and endocapillary loop fibroin thrombi (no glomerulus on the sample for immunofluorescence study). The patient temporarily improved with plasmapheresis and methylprednisolone pulses followed by high dose oral prednisone (50 mg/day). From September 1998 to January 1999, proteinuria increased to 5.4 g daily, and a high serum cryoglobulin concentration was then first detected with the assay described below (table 1). Azathioprine was replaced by monthly intravenous cyclophosphamide (1 g per infusion), associated with subsequent plasmapheresis in January and April 1999. Despite this treatment the patient’s symptoms persisted and renal complications worsened, with a raised proteinuria at 6.28 g/day and a serum creatinine at 192 µmol/l in July 1999. A new evaluation was made. A bone marrow biopsy was normal. The skin biopsy showed leukocytoclastic vasculitis with slight

2 Sharpe M, Hawton K, Pasvol G. Experience in the United Kingdom shows similar results, including better understanding of symptoms, improved communication with medical staff, and increased use of exercise and relaxation techniques. Probably most importantly of all, self management programmes significantly decrease pain, fatigue, and anxiety.

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Table 1  Evolution of cryoglobulinaemia, rheumatoid factor, and complement levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Cryoglobulinaemia (µg/ml)</th>
<th>Type</th>
<th>Rheumatoid factor (Rose-Waaler test)</th>
<th>C4 (g/l)</th>
<th>CH50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1994</td>
<td>29</td>
<td>Oligoclonal IgM</td>
<td>0</td>
<td>&lt;0.06</td>
<td>40</td>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td>1 / 128</td>
<td>&lt;0.06</td>
<td>25</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td>ND</td>
<td>&lt;0.06</td>
<td>&lt;20</td>
</tr>
<tr>
<td>December 1996</td>
<td>188</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;0.07</td>
<td>&lt;20</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td>1 / 128</td>
<td>0.10</td>
<td>50</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>November 1998</td>
<td>110†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>December 1998</td>
<td>166†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>February 1999</td>
<td>1031†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>March 1999</td>
<td>1000†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>April 1999</td>
<td>273† (after plasmapheresis)</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>1/128</td>
<td>0.09</td>
<td>30</td>
</tr>
<tr>
<td>May 1999</td>
<td>848†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Normal <15 µg/ml.
†Determination performed using the method described above since November 1998.
‡Normal range 60–120%.
To conclude, patients with clinical and biological manifestations suggestive of cryoglobulins constitute a pitfall for clinicians and biologists when standard laboratory investigations remain negative for cryoglobulinemia. Unusual in vitro properties of cryoglobulins, including dependence upon calcium concentration, should be looked for in such circumstances.

We thank Ray Langford for reviewing the English manuscript.

Correspondence to: Dr Aumaitre


Table 1 Clinical characteristics of the patients with RA and BMD values obtained (n=39). Values are expressed as mean (SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA</th>
<th>BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.2 (8.3)</td>
<td>13.3 (7.5)</td>
</tr>
<tr>
<td>Duration of postmenopausal period (y)</td>
<td>9.7 (6.4)</td>
<td>0.840 (0.150)</td>
</tr>
<tr>
<td>Erosive RA (n)</td>
<td>16</td>
<td>0.560 (0.110)</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>32</td>
<td>0.390 (0.090)</td>
</tr>
</tbody>
</table>

BMD = bone mineral density.

Computed digital absorptiometry of the hand: screening method of bone loss in postmenopausal women with RA

Dual energy x ray absorptiometry (DXA) is the most commonly used method of measuring bone mineral density (BMD). It has been shown to be a good predictor of the future risk of fracture. Unfortunately, the generalised use of DXA is limited as it is expensive and time consuming, is not portable, and is available only in specialised clinics.

Computed digital absorptiometry (CDA) of the hand is a new bone densitometry technique, designed to assess the BMD of the middle phalanx of the third finger using a direct, automated measurement of x ray attenuation. This technique is similar to radiographic absorptiometry but provides immediate results; in current radiographic absorptiometry, radiographs are sent to an off site processing centre and the results are received a few days later. CDA is cheap and quick. Its precision and accuracy seem to be acceptable, but its ability to discriminate between patients with osteoporosis and normal subjects, to predict the risk of future fracture, and to monitor the response to therapeutic intervention has not been established.

Rheumatoid arthritis (RA) is a risk factor for osteoporosis. The available data suggest that there is an increased risk of hip fracture in patients with RA, especially when they are treated with glucocorticoids. DXA is the preferred technique for assessing the presence of bone loss in these patients. However, the prevalence of RA in the general population is high, and it is, therefore necessary to use DXA to investigate only those patients at high risk of osteoporosis. Criteria to decide who should be evaluated are currently not available. Recently, in this journal, Lems and Dijkmans presented a proposal from rheumatologists in Amsterdam based on clinical risk factors.

We have undertaken a study to evaluate whether CDA might be a useful screening technique for identifying the patients with RA who should be examined by DXA. Over a period of three months all postmenopausal women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria were asked to participate. The inclusion criteria were (a) duration of RA longer than one year, (b) duration of postmenopausal period longer than one year, and (c) no current treatment with bone thinning agents.

Forty-five patients fulfilled the inclusion criteria and consent was obtained from 40 of these. In these patients BMD was assessed by DXA and CDA on the same day. One further patient was not included in the study as she had a severe ulnar deviation that did not allow CDA to be used. For DXA, BMD (g/cm²) of the lumbar spine and upper femur was assessed using a dual energy x ray system (Hologic QDR 1000, Hologic Inc, Waltham, Mass); we considered the mean value of the L2–4 vertebrae and the value of the femoral neck. For CDA, BMD (g/cm²) of the middle phalanges of the third finger of the non-dominant hand was assessed using a dual energy x ray system (AccuDEXA, Schick Technologies, Long Island, NY). The x ray attenuation was automatically processed and represented as a grey scale image. To assess the in vivo short term precision, 10 serial measurements (with interim repositioning) were performed in seven healthy volunteers. The in vivo precision of AccuDEXA, expressed as a coefficient of variation, was 1.16% (0.74 to 1.56). Data were cross referenced with the T score. According to WHO criteria, osteoporosis is defined as a T score below −2.5.

A Spearman correlation test and linear regression analysis were used to test the relation between the variables; p<0.05 was considered significant. A 2x2 table was used to evaluate the positive and negative predictive value of CDA for the diagnosis of osteoporosis established by DXA.

Table 1 lists the clinical characteristics of the patients and the mean BMD values obtained. BMD at the lumbar spine and at the non-dominant hand correlated significantly (r = 0.51, p<0.01). Similarly, BMD at the femoral neck and at the non-dominant hand were significantly correlated (r = 0.51, p<0.01).

DXA showed that 13 patients had osteoporosis and CDA that 16 patients had the disease in at least one of the evaluated zones. The positive predictive value of CDA for the diagnosis of osteoporosis was 56%. The negative predictive value for the diagnosis of osteoporosis was 83%.

The correlations found between BMD at the non-dominant hand and BMD at the lumbar spine and femoral neck were moderate. A negative predictive value of 56% was considered acceptable. Our results suggest that CDA could be a screening method used to decide which patients with RA should be investigated for osteoporosis. Further investigations are needed to confirm our findings.

1 WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organisa-


5 Cooper C, Coupland C, Mitchell M. Rheuma-


Rubella infection in adult onset Still's disease

The aetiology of adult onset Still's disease remains unknown although some authors have tried to relate it to a viral infection. In our case we think that rubella was more probably attributable to a reinfection than to a primary infection because the patient had been correctly vaccinated in childhood and this is also supported by the increase in IgG antibody titre without increase in IgM concentration. The reason for the seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other rubella antibody titres.

Although aetiology of adult onset Still's disease is unknown, some authors have tried to demonstrate that infective agents, especially viruses, can be the trigger of the illness in susceptible patients. 

Inflammatory disease because there was no non-specific stimulation after a generalised inflammatory disease and viral infections. 


Valtonen JO, Kosunen TU, Karjalainen J, Valtonen M, Lennarz-Reijo M, Valtonen VV. Seroepidemiology of parvovirus B19 infection with acute syn


Raised plasma adrenomedullin in patients with systemic sclerosis complicated by pulmonary hypertension

Adrenomedullin is a hypotensive peptide newly found in human rhechoomocytoma tissue. The peptide comprises 52 amino acids with an intramolecular disulphide bond. The mRNA of adrenomedullin has been detected in normal adrenal medulla, heart, kidney, and lung. Adrenomedullin is produced in endothelial cells, vascular smooth muscle cells, and bone marrow cells. Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasorelaxant effect, antagonizing the vaso
pastic effect of endothelin-1 and seems to be implicated in the physiological and pathological control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure, in particular, by inhibiting the production of a chemotactic attractant from alveolar macrophages.

Systemic sclerosis (SSc) is a chronic disease of unknown cause characterised by vascular changes and fibrosis of the skin and the visceral organs. Major complications of SSc are renal, myocardial, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc. Increased plasma of patients with PH the endothelin-1 level is raised. In addition, it was recently reported that the adrenomedullin level is raised also in the plasma of patients with Raynaud's disease or rheumatoid arthritis. Therefore, we measured the concentrations of adrenomedullin and endothelin-1 in the plasma from patients with SSc, with or without PH, to elucidate the role of adrenomedullin in the pathogenesis of PH.

We obtained plasma from three women with SSc with PH (aged 43–72), 10 patients with SSc without PH (nine women, one man, aged 22–60), and one female patient with primary PH. The diagnosis of SSc was based on accepted criteria. We diagnosed PH in...
patients with SSc whose right ventricular systolic pressure was higher than 25 mm Hg measured by echocardiogram. In the three patients with SSc with PH we confirmed PH by catheterisation. The pressures of the pulmonary artery of these three patients were 45, 51, and 54 mm Hg, respectively. All patients with SSc had diffuse-type SSc without interstitial pneumonia, which was diagnosed as interstitial fibrosis by computed tomography. The three patients with PH were taking the following drugs: trifluperidol hydrochloride (patient 1), nifedipine and trifluperidol hydrochloride (patient 2), and nicardipine hydrochloride and methylprednisolone (patient 3).

For the comparison group we selected patients with diffuse-type SSc without PH, as all of three patients with SSc with PH had diffuse-type SSc. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunoassay. Statistical significance was analysed with the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in those with SSc without PH (p = 0.011) or than in normal volunteers (p = 0.020) (fig 1A). The concentrations of adrenomedullin or endothelin-1 in the plasma from a patient with PH was significantly higher in patients with SSc with PH than in healthy volunteers (p=0.011).

Our results suggest that the amount of adrenomedullin is insufficient to inhibit either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats.1 This highlights the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

Avascular necrosis of a single vertebral body, an atypical site of disease in a patient with SLE and secondary APS

Antiphospholipid syndrome (APS) is characterised by recurrent arterial or venous thrombosis. Deep veins, such as the femoral and popliteal veins are by far the commonest sites of thrombosis. The arterial and venous systems of the mesenteries, liver, kidneys and the adrenal glands are also involved.2 We report here a 39 year old woman with systemic lupus erythematosus (SLE) and secondary APS who presented with subacute onset of back pain and was found to have avascular necrosis (AVN) of a single vertebral body at L2, an atypical presentation of this complication.

In 1976, a 17 year old white woman complained of gastrointestinal upset and frequent joint pain in her hands and knees a few months after she started taking oral contraceptives. She was found to have Coombs’ positive haemolytic anaemia, leucopenia, thrombocytopenia and deranged liver function. Serologically, she had positive anti-nuclear antibody (ANA, 1/1280 on rat liver cells), anti-double stranded (ds) DNA antibodies (1/320 on Crithidia luciliae) and posi-

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**Figure 1** Concentrations of (A) adrenomedullin and (B) endothelin-1 in plasma. Short horizontal lines = 10th and 90th centiles; long horizontal lines = 25th, 50th, and 75th centiles; the circles denote the value outside 10th and 90th centiles in patients with SSc with and without (−) pulmonary hypertension (PH), and normal volunteers. ND = not done.
tive anti-thyroid micorsomal antibodies. Antibodies to the extractable nuclear antigens (ENA) were negative. Liver biopsy showed features compatible with chronic active hepato-

titis. SLE with an associated hepatitis was diagnosed and she was prescribed predni-
solone 15 mg daily, which was gradually reduced over two years as her liver function and platelet count stabilised. Over the next four years, she developed recurrent deep ven

thrombosis in her left popliteal, left femoral and hepatic veins. She had three spontaneous abortions, all early in the second trimester. Subsequent investigations showed a positive lupus anticoagulant (LAC) and IgG anti-
cardiolipin antibody (ACA). She was treated with warfarin for 20 years. In 1980, she developed a migranous headache, fever and polyarthralgia and was diagnosed as having a flare of her underlying lupus and secondary APLS.

She was given corticosteroids with satisfac-
tory response and she was later maintained with azathioprine while the oral prednisolone dose was gradually brought down to 10 mg daily. She was also given dipiridamole, an anti-platelet agent, and atenolol for hyperten-
sion that was diagnosed during subsequent follow ups but there was no other evidence of renal involvement. Calcium supplements and vitamin D were started for prophylaxis against osteoporosis. She had another flare of her SLE in October 1988 when she was presented with polyarthralgia and significant thrombo-

cytopenia. Her warfarin was stopped in view of her SLE in October 1988 when she presented with polyarthralgia and significant thrombo-

cytopenia. Her warfarin was stopped in view of the potential increase risk in bleeding ten-
dency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was per-
formed, after which her platelet count sta-

blished. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with pred-
sisolone (5-10 mg/day) and azathioprine until April 1998 when she complained of constant and severe back pain, which was aggravated by movement. A plain radiograph showed no obvious abnormality but magnetic resonance imaging of the thoracicobarum spinar showed features suggestive of bone inf-

action of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AYN. Figure 1 shows the plain radiogra-

phic view of the lumbosacral spine. Fig-

ure 2 shows the T2 weighted magnetic reso-

nance sagittal image of the lumbosacral spinar spine with increase in signal over the L2 vet-

tebal body as referred to the orthopaedic surgery unit for a L1 to L3 vertebral fusion. Histological examination of the in-

volved site showed bone necrosis and features compatible with AYN. Her back pain was much improved after the operation. She has all along been normotensive and she has no hyperlipidaemia.

In summary, this patient suffering from SLE with secondary APLS who has been maintained with low dose corticosteroids for more than 20 years was complicated by the development of AYN at an atypical site.

This case highlights two interesting points. The first is the atypical presentation of the AYN involving an isolated L2 vertebral body. Vertebral body involvement by APLS is seldom reported. Egan et al reported on a patient with catastrophic APLS who pre-

sented with a new onset of AYN involving multiple sites including T8, L4 and L5 verte-

bral bodies in 1994. Bone marrow necrosis without bony destruction has also been reported to be associated with APLS, usually in the context of catastrophic APLS and picked up by bone scan as multiple hot

spots. The lunate bone is another unusual site of involvement by AYN. Kienbock’s disease (AVN of lunate bone) was reported in a patient with primary APLS and two others with antiphospholipid (APL) antibodies but without other clinical features that satisfied the diagnosis of APLS.

Secondly, the pathogenesis of AYN is complex. AYN is a known complication of various systemic conditions including sickle cell disease, prolonged corticosteroid treatment, alcohol abuse and Gaucher’s disease. When occurring in the hip, it is commonly seen in elderly patients after fracture neck of femur, as a result of disturbance to its blood supply. Previous studies in patients with SLE have suggested high dose and prolonged use of corticosteroids causes AYN. Active disease and the presence of APL antibodies may also have important roles in the development of AYN in these patients. It is interesting that our patient had features of secondary APLS with previous venous thrombosis and recur-

rent fetal abortion. Additionally, she had a relapsing and remitting disease that required the prolonged use of corticosteroids for disease control. Whether the presence of APL antibodies, active disease, or the prolonged use of corticosteroids, or all three, led to AYN of her L2 vertebral body is unclear. In view of this, we have recently performed a case-

control study to evaluate the role of each of these individual potential risk factors.

In summary, this patient suffered from catastrophic APLS and AYN, the latter being a complication of the former. We have reviewed the literature on AYN in SLE and catastrophic APLS. The patient responded well to treatment with prednisolone (5-10 mg/day) and azathioprine. Streptokinase was used for thrombosis in the left popliteal, left femoral and hepatic veins. The patient has been followed up for 9 years and has had no other episodes of AVN.

In conclusion, we believe that AYN is a rare but significant complication of SLE and catastrophic APLS. The treatment of AYN should be aggressive and multidisciplinary, involving the rheumatologist, cardiologist, neurologist and orthopaedist.

Comparison of patients with and without adverse reactions.

Values are shown as mean (SD)

<table>
<thead>
<tr>
<th>IgG†</th>
<th>With adverse reaction (n)</th>
<th>Without adverse reaction (n)</th>
<th>p Value‡</th>
<th>Threshold value</th>
<th>p Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 20.87 (7.34)(15)</td>
<td>20.12 (5.90)(83)</td>
<td>NS</td>
<td>4.62</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−6.23 (3.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>***</td>
<td>0.171</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre/pre</td>
<td>−0.30 (0.13)(15)</td>
<td>−0.06 (0.16)(81)</td>
<td>NS</td>
<td>0.189</td>
<td>***</td>
</tr>
<tr>
<td>IgA†</td>
<td>Pre 4.50 (2.17)(15)</td>
<td>4.13 (1.61)(83)</td>
<td>NS</td>
<td>0.83</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−1.55 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>***</td>
<td>1.08</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre/pre</td>
<td>−0.31 (0.14)(15)</td>
<td>−0.03 (0.18)(81)</td>
<td>NS</td>
<td>0.189</td>
<td>***</td>
</tr>
<tr>
<td>IgM‡</td>
<td>Pre 2.03 (0.86)(15)</td>
<td>2.04 (0.84)(83)</td>
<td>NS</td>
<td>0.26</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/d)</td>
<td>−0.77 (0.60)(15)</td>
<td>−0.15 (0.44)(81)</td>
<td>***</td>
<td>0.257</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre/pre</td>
<td>−0.35 (0.17)(15)</td>
<td>−0.07 (0.17)(81)</td>
<td>NS</td>
<td>0.257</td>
<td>***</td>
</tr>
<tr>
<td>γ Globulin</td>
<td>Pre 15.64 (7.00)(13)</td>
<td>15.54 (4.69)(74)</td>
<td>NS</td>
<td>2.38</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−5.07 (3.61)(12)</td>
<td>−1.30 (2.22)(74)</td>
<td>NS</td>
<td>2.38</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre/pre</td>
<td>−0.30 (0.15)(12)</td>
<td>−0.08 (0.16)(74)</td>
<td>NS</td>
<td>2.243</td>
<td>***</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Pre 1.82 (0.80)(15)</td>
<td>1.38 (0.61)(81)</td>
<td>NS</td>
<td>0.18</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre (10⁹/l)</td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>NS</td>
<td>0.267</td>
<td>***</td>
</tr>
<tr>
<td>Post−pre/pre</td>
<td>−0.35 (0.31)(14)</td>
<td>0.12 (0.71)(80)</td>
<td>NS</td>
<td>0.267</td>
<td>***</td>
</tr>
</tbody>
</table>

CRP from 63 (36) to 32 (55) mg/l, whereas all 22 non-responders who had no adverse events showed a decrease in CRP by 46 (39) to 41 (34) mg/l. A significant relation was found between a good response to treatment and the appearance of adverse reactions. The patients with adverse reactions had a higher creatinine level, and more frequent consumption or leakage of immunoglobulin fractions, and lymphocyte count in the admission. The reduction in lymphocyte count was suggestive of toxicity. Conversely, in patients without adverse reactions, the decreases were less than 20%. The clinical improvement contributed only partially to the reductions; steroid treatment was not likely to have been the cause either, as they had been given for a long time without a significant change in the dose.

Recently, we reported that the immunoglobulin levels decrease with adverse reactions, during a disease modifying antirheumatic drug, bucillamine, treatment. A reduction in interleukin 6 level was reported to parallel an improvement during methotrexate treatment. The reduction in lymphocyte numbers is controversial. Immuno-modulation might relate mainly to adverse reactions, whereas the effect might appear owing to anti-inflammatory mechanisms. It can only be speculated whether consumption or leakage of immunoglobulin plays a part in the previously supposed mechanism of acute hypersensitivity or cytotoxicity, or in an independent epigenetic phenomenon. There is the encouraging possibility that monitoring the immunoglobulin level and the lymphocyte count might disclose life threatening reactions and enable the doctor to know when to reduce the dosage or to stop the drug entirely.

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