How should we manage fibromyalgia?

We read with interest your leader, “How should we manage fibromyalgia?” We were puzzled by Paul Reilly’s statement that a comprehensive pain management programme has the best chance of success, although even rheumatologists can practise amateur cognitive behaviour therapy in the clinic. Is Dr Reilly really suggesting that a rheumatologist’s amateur efforts offer 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. 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 circle of 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 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.

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.

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 effective courses encourage people to take control for themselves be a welcome adjunct to his treatment, even if it is run by a patient self-management group?

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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 cryoglobulinaemia may manifest clinically as skin, articular, renal, and peripheral nerve complications. To ensure optimal detection, serum samples must be obtained and preserved at 37 °C. We report on a patient whose clinical presentation was suggestive of cryoglobulinaemia. Because cryoglobulins had been either undetectable or found at very low levels for 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 cryoglobulinaemia. Included below is a description of the method used for cryoglobulin detection, emphasising the importance of in vitro calcium concentration.

Case report

A 52-year-old man with multiple lipomas had a 20-year history of polyarthralgia 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, which was diagnosed as celiac disease. In June 1996 he developed attacks of abdominal pain concomitantly with arthralgias 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 1.03–3.31). Some of the rheumatoid factors, including the Rose-Waaler test (Sanoft Pasteur, Marnes La Coquette, France), were positive (table 1), but other autoantibodies remained negative, including antinuclear, and anti-DNA and antineutrophil cytoplasmic antibodies.

Complement concentrations were notably decreased, both for C4 <0.06 g/l (normal range 0.60–1.10) and C3 <0.04 g/l (normal range 0.10–0.40). Behring/Dade, Deerfield, USA) and for C4 (home method) 25% of the normal range (60–120%). C3c and C3PA were also decreased at respectively 0.34 g/l (normal range 0.60–1.10) and <0.04 g/l (normal range 0.10–0.40). A complete set of serum markers were negative 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, plasma exchange 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 flare up occurred in August 1998, which was treated with 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
deposits of IgM, IgA, and C3 on immunofluorescence study. Renal biopsy showed an endocapillary and extracapillary glomerulonephritis with glomerular crescents in a mean of 30% of glomeruli, and IgG, IgM, and C3 deposits on immunofluorescence study. Prednisone was continued and cyclophosphamide was given orally (150 mg/day). The patient’s condition is stabilised at the present time.

A modified assay was developed to detect a possible cryoglobulin. Briefly, a serum sample was obtained and centrifuged at 37 °C, then stored at 4 °C for eight days. The precipitate was separated by centrifugation, then washed each day for three consecutive days with either cold phosphate buffered saline (PBS; conventional assay) or distilled water to enhance the protein solubility (current assay). Indeed, we noted that some of the precipitate was lost in the PBS. Then, each precipitate was dissolved in a low volume of PBS for measurement of protein (Hartree observation) and typed by Western blot (fig 1).† Precipitates obtained by both methods were analysed with two dimensional polyacrylamide gel electrophoresis.† In addition, some cryoprecipitate samples were passed at 37 °C over protein G-Sepharose columns. Proteins were then eluted using HCl-glycine, pH 2, and analysed with two dimensional polyacrylamide gel electrophoresis. The influence of calcium concentration on cryoglobulin solubility was investigated as follows. Solubility of the cryoglobulin obtained with distilled water was tested by adding Hank’s solution containing either Ca2+ (1.26 mM) and Mg2+ (0.80 mM), Ca2+ (1.26 mM) without Mg2+, or Mg2+ (0.80 mM) without Ca2+. The dissolved proteins were measured as described above. About 50% of the precipitate became soluble when Ca2+ was present in the milieu, contrasting with 5% solubility only when Ca2+ was absent.

Our observation indicates that cryoglobulinaemia must remain highly suspected despite apparently negative laboratory results when clinical and biological data—namely, low C4 associated with positive rheumatoid factors—are consistent with, or even more suggestive of this diagnosis. Indeed, monoclonal or polyclonal rheumatoid factors are nearly always part of mixed cryoglobulins, where they bind to immune complexes—principally antigen complexed IgG—that subsequently precipitate.† Nevertheless, when using conventional assay, cryoglobulin remained negative or weakly positive in our patient. Interestingly, a monoclonal IgMx was sometimes found on immunofixation analysis. In November 1998 the occurrence of glomerulonephritis consistent with cryoglobulin related kidney complications prompted us to perform further tests for cryoglobulins, including the method described above. Then, a high titre type II cryoglobulin (>1000 μg/ml) was isolated, and subsequently shown to consist of monoclonal IgMx and polyclonal IgG, the former being thought to support the previously detected rheumatoid factor activity. Two dimensional polyacrylamide gel electrophoresis confirmed the presence of polyclonal IgG and monoclonal IgMx in the cryoprecipitate, and allowed identification of an additional monoclonal IgA. Finally, electrophoretic studies of the proteins eluted from protein G columns showed the presence of polyclonal IgG, with only traces of the monoclonal IgMx, indicating that the complex dissociated at 37 °C.

This cryoglobulin has unusual properties because it became soluble in PBS, while it precipitated in serum, distilled water, or calcium buffers. Usually, cryoprecipitation is a two step process. First, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondly, the large immune complexes precipitate. This requires favourable physicochemical conditions, including suitable pH and ionic strength of the solvent. Usually, the precipitate is stable in saline. Our data suggest that calcium concentration may be crucial for cryoglobulin precipitation, as in the case reported by Qi et al.* This property might account for some of the discrepancies observed between the conventional and the current assay. It might also explain the severity of the symptoms in vivo. Further investigation is needed to approach the other determinants of precipitation. Hypocryoglobulins display a quite different property in the way they are isolated from hypotonic serum, though they lead to the same clinical syndrome.†

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></td>
<td>0</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td></td>
<td>1/128</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td></td>
<td>ND</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>December 1996</td>
<td>188</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td></td>
<td>1/128</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>November 1998</td>
<td>1108†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>December 1998</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>February 1999</td>
<td>1031†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>0.08</td>
</tr>
<tr>
<td>March 1999</td>
<td>1000†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>0.09</td>
</tr>
<tr>
<td>April 1999</td>
<td>273† (after plasmapheresis)</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>0.30</td>
</tr>
<tr>
<td>May 1999</td>
<td>848†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Normal <15 µg/ml.
†Determination performed using the method described above since November 1998.
‡Normal range 60–120%.

Figure 1 Western blot of cryoglobulin. Pattern obtained with anti IgG, IgA, IgM, κ and λ chains labelled with alkaline phosphatase on cryoglobulins transfused onto nitrocellulose sheets: oligoclonal (top) and polyclonal pattern (middle) for cryoglobulin washed with conventional assay, type II pattern IgMx (arrow) and polyclonal IgG, IgA, and IgM for cryoglobulin washed with current assay (bottom).
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.

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**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></td>
</tr>
<tr>
<td>Rheumatoid factor positive (%)</td>
<td>80.00 (0.150)</td>
<td></td>
</tr>
<tr>
<td>Erosive RA (%)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
<td>0.840 (P = 0.150)</td>
<td></td>
</tr>
<tr>
<td>BMD at the femoral neck (g/cm²)</td>
<td>0.560 (P = 0.110)</td>
<td></td>
</tr>
<tr>
<td>BMD at the middle phalanx of the third finger (g/cm²)</td>
<td>0.390 (P = 0.090)</td>
<td></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, and 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 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 examined by DXA vary between patients with osteoporosis and normal subjects, to predict risk of future fracture, and to monitor the response to therapeutic intervention has not been established.

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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 DXA 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 phalanx 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 data were 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 2×2 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 of CDA 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 CDA 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.
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. We describe here a case of typical adult onset Still’s disease with a seroconversion in the rubella IgM antibody titre to emphasise that this is probably more than a coincidental event. A 26 year old woman was admitted because of fever with chills, a pruritic rash, myalgia, sore throat and headache. At the time of admission examination the temperature was 40°C and the pulse rate 104 beat/min. The rash consisted of small pruritic macules over back, periorbicular, legs and arms. The patient was erythematous. Some small cervical lymphadenopathies were detected. The leucocyte count was 42,3 × 10^9 cells/l (93.2% neutrophils) and the haemoglobin concentration was 79 g/l. Liver enzymes were slightly increased, aspartate aminotransferase (AST) 0.80 µkat/l and alanine aminotransferase (ALT) 0.73 µkat/l, but increased to AST 11.77 µkat/l and ALT 7.68 µkat/l after acetylsalicylic acid administration. Lactate dehydrogenase was 17.33 µkat/l. The serum albumin concentration was 26 g/l and the erythrocyte sedimentation rate 60 mm 1st. The serum ferritin was higher than 1500 µg/l (normal value: 20–250 µg/l). Roentgenogram of chest and urine analysis were normal as well as blood and urine cultures. Abdominal computed tomography showed hepatosplenomegaly. An electromyographic study was normal. Tests for antinuclear antibodies and rheumatoid factor were negative. Serum concentrations of immunoglobulins and complement were normal. Serological tests for hepatitis A, B or C, cytomegalovirus, parvovirus B19, human immunodeficiency virus 1 and 2, Epstein-Barr virus, Mycoplasma, Treponema pallidum, Borrelia burgdorferi, Toxoplasma, Salmonella, Brucella, Legionella, Coxiella burnetti, Chlamydia and Rickettsia were negative. The initial rubella IgM antibody titre was 140 000 IU/l. During admission the patient looked acutely ill. Temperature rose to 40°C every evening with chills. The patient developed swelling and tenderness of interphalangeal joints, elbows, wrists and knees. Roentgenograms of joints were normal. Because of cough a new chest roentgenogram was made. It showed a right basal lobe alveolar infiltrate that resolved spontaneously in 72 hours.

At this point, our patient fulfilled the criteria of Yamaguchi for adult onset Still’s disease. Initially, she was treated with acetylsalicylic acid 4 g/day by mouth, which had to be stopped because of an increase in liver enzymes, so prednisone 1 mg/kg/day was added to diminish arthritis. The dose achieved was 7.5 mg by mouth weekly. The patient was discharged feeling well after staying in hospital for 34 days. At this moment rubella IgG antibody titre rose to 660 000 IU/l.

Our patient fulfilled Yamaguchi’s criteria for adult onset Still’s disease so this diagnosis was admitted. There was also strong evidence for acute rubella infection because the IgG antibody titre increased more than fourfold the initial one. It has been shown that children with primary rubella infection developing Still’s disease increase both rubella IgG and IgM antibody titres. In our case we think that rubella was more probably attributable to a reactivation 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. This seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other infectious 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, myxovirus, eohovirus, 7, mumps, cytomegalovirus, 8 para-influenza, 9 Epstein-Barr virus, 10 influenza A, 11 parvovirus B19, 12 hepatitis B or C 13 and rubella 14 have been associated.

The relation between rubella virus and adult onset Still’s disease has been reported in some series and case reports since the initial description by Bywaters in 1971. Wouters et al performed exhaustive virological studies in patients with adult onset Still’s disease in an early phase of the illness and found evidence of viral infection in three cases, two of them corresponding to rubella. The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still’s disease. In summary, we think that the increased rubella IgG antibody titre in our patient should not be considered an anecdotal event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports, 14 supports the hypothesis about the role of viruses in the aetopathogenesis of adult onset Still’s disease.

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

Adrenomedullin is a hypotensive peptide newly found in human pheochromocytoma 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 vascular smooth muscle 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 pathologi- cal control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure, and to exert a vasodilator effect on the cardiovasc- ular system. Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating cAMP formation in a receptor-dependent manner, and exerting an anti-inflammatory effect by inhibiting the production of a chemotact- ant 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. Plasma levels of adrenomedullin in 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 7 or rheumatoid arthritis. 8 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. 9 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 and PH we confirmed that 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: triclopidine hydrochloride (patient 1), nifedipine and triclopidine 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 and 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 healthy volunteers (p = 0.011). The levels of adrenomedullin in patients with SSc and PH were raised compared with those in patients with SSc without PH (p = 0.020) (fig 1A). The concentrations of adrenomedullin or endothelin-1 in patients with SSc and PH were raised compared with those in patients with SSc without PH (p = 0.041) (fig 1B). We did not measure levels of endothelin-1 in normal volunteers (fig 1B).

We recently obtained similar results when measuring the levels of the mature form of adrenomedullin and total adrenomedullin in a different group of patients with SSc with (patients 4, 5, and 6) or without PH, by immunoradiometric assay. The three patients with SSc with PH were women aged 43–54, and two patients with SSc without PH were women aged 47 and 55. The duration of disease was two to seven years. The pulmonary artery pressures of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively. The levels of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5, respectively, whereas those of the two patients with SSc without PH were 16.4 and 14.7 pg/ml. These results, however, did not reach statistical significance as the number of patients was small.

Patients 4, 5, and 6 were taking the following drugs: nifedipine, tocopherol acetate, and beraprost sodium (patient 4); nifedipine and triclopidine hydrochloride (patient 5); and nifedipine (patient 6). Levels of adrenomedullin in the plasma were 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 either suppress 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. Thus our results also suggest the possibility that interventions aimed at controlling the balance of adrenomedullin and endothelin-1 might prove fruitful in preventing PH in patients with SSc.

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.

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

Antiphospholipid syndrome (APLS) 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.1 We report here a 39 year old woman with systemic lupus erythematosus (SLE) and secondary APLS 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 antibody (1/320 on Crithidia lucidae) and posi-
tive anti-thyroid microsomal antibodies. Antibodies to the extractable nuclear antigens (ENA) were negative. Liver biopsy showed features compatible with chronic active hepatitis. SLE with an associated hepatatis was diagnosed and she was prescribed prednisolone 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 vein 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. She was pregnant in 1980, she developed menegran in migraine, fever and polyarthralgia and was diagnosed as having a flare of her underlying lupus and secondary APLS.

She was given corticosteroids with satisfactory response and she was later maintained with azathioprine while on prednisolone 5–10 mg/day and azathioprine while the oral prednisolone was gradually brought down to 10 mg daily. She was also given dipenidramole, an anti-platelet agent, and anestolol for hypertension 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 presented with polyarthralgia and significant thrombocytopenia. Her warfarin was stopped in view of the potential increase risk in bleeding tendency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was performed, after which her platelet count stabilised. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with prednisolone (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 thoracolumbar spine showed features suggestive of bone infarction of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AVN. Figure 1 shows the plain radiograph of the lumbar spine. Figure 2 shows the T2 weighted magnetic resonance sagittal image of the thoracolumbar spine with increase in signal over the L2 vertebral body. She was referred to the orthopaedic surgery unit for a L1 to L3 vertebral fusion. Histological examination of the involved site showed bone necrosis and features compatible with AVN. 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 had been managed with low dose corticosteroids for more than 20 years was complicated by the development of AVN at an atypical site. This case highlights two interesting points. The first is the atypical presentation of the development of AVN at an atypical site. More than 20 years was complicated by the maintained with low dose corticosteroid for all along been normotensive and she has no hyperlipidaemia. She was referred to the orthopaedic surgery unit for a L1 to L3 vertebral fusion. Histological examination of the involved site showed bone necrosis and features compatible with AVN. Her back pain was much improved after the operation. She has all along been normotensive and she has no hyperlipidaemia.

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CRP from 63 (36) to 32 (55) mg/l, whereas all 22 non-responders who had no adverse events showed a decrease in CRP from 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 use of steroid at high dose (7.9 (7.0) vs 2.8 (3.5) mg/day prednisolone). The patients with the higher creatinine level were older.

The albumin level increased more in responders. The rheumatoid factor titre decreased in responders and in patients without adverse reactions. The eosinophil count did not correlate either with response or adverse reactions.

After treatment the levels of IgG, IgA, and IgM, γ fractions, and lymphocyte count in the 15 patients who had adverse reactions were significantly reduced compared with the values before treatment. The reductions and reduction ratios with pretreatment values were significantly greater in patients with adverse reactions than in those without. Table 1 gives the results obtained and the threshold values that could differentiate between patients with and without adverse reactions. When the patients were grouped according to therapeutic response, significant reductions were seen only in the levels of immunoglobulins and γ fractions, but no reduction was seen in lymphocyte counts, in 14 patients. The greater decreases in responders than in non-responders were seen only in IgG and IgA levels. The reductions and reduction ratios of immunoglobulins were greater in patients with adverse reactions, grouped according to toxicity (30–35%, Table 1), than in those with therapeutic response grouped according to efficacy (13–14%, data not shown).

Our study shows that when a patient’s immunoglobulin levels and lymphocyte count decrease globally by as much as 25% or more from the pretreatment level, this decrease is 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 level decreases 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. Immunomodulation 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 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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