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, must 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-behavioural 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 objectivity 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. The objectives and the objectives of such a group and worse prognosis in cases such as ours, which encourage people to take control for themselves—and which

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 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.

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 his 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 cryoglobulinemia may manifest clinically as skin, articular, renal, and peripheral nerve complications.1 To ensure optimal detection, cryocrit samples must be obtained and preserved at 37 °C. We report on a patient whose clinical presentation was suggestive of cryoglobulinemia. Because cryoglobulins were 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 cryoglobulinemia. Included below is a description of the method used for cryoglobulin detection, emphasizing the importance of in vitro calcium concentration.

Case report

A 52-year-old man with multiple lipomas had a 20-year history of polyarthralgias 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 legs and ankles. 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 1.08–2.35). Unlike the rheumatoid factors, including the Rose-Waaler test, antinuclear, antikeratinocyte, and DNA and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C4 <0.06 g/l (normal range 0.10–0.40) and for CH50 (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 serological markers was negative, including HBV 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, with increased proteinuria and calciuria. 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 proteinuria and cryoglobulins 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...
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 (% 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>
</tr>
<tr>
<td>June 1996</td>
<td>25</td>
<td>Oligoclonal IgM</td>
<td>1 / 128</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</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>ND</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td></td>
<td>1 / 128</td>
<td>&lt;20</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;20</td>
</tr>
<tr>
<td>November 1998</td>
<td>1105†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;50</td>
</tr>
<tr>
<td>December 1998</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;50</td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>&lt;50</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>
</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>
</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>30</td>
</tr>
<tr>
<td>May 1999</td>
<td>848†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</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 chain labelled with alkaline phosphatase on cryoglobulin precipitated by two-dimension polyacrylamide gel electrophoresis. Panel labelled with alkaline phosphatase (top) and polyclonal pattern (middle) for cryoglobulin washed with conventional assay, type II pattern IgM (arrow) and polyclonal IgG, IgA, and IgM for cryoglobulin washed with current assay (bottom).

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). 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 cryoglobulinemia 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 a 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 polyaconal IgG and monoclonal IgM 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 polyaconal 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 symptoms in vivo. Further investigation is needed to approach the other determinant factors 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.
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.

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**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 laboratories.

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 Dieijmans 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 of 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-L4 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 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.

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics of the patients with RA and BMD values obtained (n=39). Values are expressed as mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Duration of postmenopausal period (y)</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis (y)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (n)</td>
</tr>
<tr>
<td>Erousive RA (n)</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
</tr>
<tr>
<td>BMD at the femoral neck (g/cm²)</td>
</tr>
<tr>
<td>BMD at the middle phalanx of the third finger (g/cm²)</td>
</tr>
</tbody>
</table>

*BMD = bone mineral density.
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 IgG antibody titre to emphasise that it 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 physical 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 joints were non-swollen. Some small cervical lymphadenopahies were detected. The leucocyte count was 42.3 × 10⁹ 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 lumbosacral spine 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. The initial rubella IgG 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 proximal 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 well established. 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 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. This seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other autoantibody 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, e.g. echovirus 7, mumps, cytomegalovirus, influenza, Epstein-Barr virus, influenza A, parvovirus B19, hepatitis B or C and rubella. A and B19 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 accidental event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports, supports the hypothesis about the role of viruses in the aetopathogenesis of adult onset Still’s disease.

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Raised 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 disulfide 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 smooth muscle cells of the glomerular capillary wall. Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasorelaxant effect, antagonising 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 volumes and blood pressures in patients with pulmonary hypertension. The mRNA of adrenomedullin is also expressed in the kidney, which may be responsible for the renal effects of adrenomedullin. Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating cAMP formation in a dose-dependent manner, and exerting an anti-inflammatory effect by inhibiting the production of a chemotactic agent 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. In patients with pulmonary hypertension, 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 measured by echocardiogram. In the three systolic pressure was higher than 25 mm Hg patients with SSc whose right ventricular

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 primary PH were similar to those from patients with SSc without PH (data not shown). The levels of endothelin-1 in patients with SSc with 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 46, 59, and 60 mmHg, respectively. The levels of adrenomedullin in the plasma of patients 4, 5, and 6 were 24.9, 58.1, and 27.5 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, nicardipine hydrochloride and methylprednisolone (patient 1), nifedipine and triclopidine hydrochloride (patient 2), and nifedipine hydrochloride (patient 3). All of three patients with SSc with PH had interstitial pneumonia, which was diagnosed as interstitial fibrosis by computed tomography. The three patients with PH were taking the following drugs: ticlopidine hydrochloride (patient 1), nifedipine and triclopidine hydrochloride (patient 2), and nicardipine hydrochloride and methylprednisolone (patient 3).

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. 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 kness 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 antinuclear antibody (ANA, 1:1280 on rat liver cells), anti-double stranded (ds) DNA antibody (1:320 on Crithidia luciliae) 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 hepatitis 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 in 1980, she developed severe migranous headache, 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 she was normotensive and she has no history of previous venous thrombosis and with the presence of APL antibodies may also have important roles in the development of AVN in these patients.

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

Secondly, the pathogenesis of AVN is complex. AVN is a known complication of various systemic conditions including sickle cell disease, prolonged corticosteroid treatment, alcohol abuse and Gaucher's disease. When one patient had features of secondary APS with previous venous thrombosis and recurrent 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 causes AVN. The limiting factor in low dose pulse methotrexate treatment for rheumatoid arthritis (RA) has been its toxicity. We recently treated a female patient with RA, in whom pneumonitis and granulocytopenia developed during methotrexate treatment; her white blood cell count was 1.10×10^9/l and Pao, was 37 mm Hg. Before treatment, at the time of development of adverse reactions, and after recovery after methotrexate was withdrawn, her IgG levels were 17.99, 10.15, 16.75 g/l; IgA 5.14, 3.69, 4.33 g/l; IgM 1.73, 1.06, 3.36 g/l; and lymphocyte count 1.96, 0.42, 1.56×10^9/l, respectively. We then investigated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate treatment develop.

One hundred consecutive patients with RA (80 women and 20 men, mean (SD) age 57.5 (9.2) years) receiving between 2.5 and 15 mg of methotrexate weekly in Tokyo Metropolitan Komagome Hospital were followed up from 1991 to 1998. When the patients did not respond and had no adverse reactions, the dose was increased by 1.25 to 2.5 mg/week. Response to treatment, assessed by the patient's impression of improvement, a decrease in swelling and pain of more than two joints, a decrease of >20 mg/l in the CRP level, adverse reactions, lymphocyte and eosinophil counts, serum concentrations of immunoglobulins, fraction, rheumatoid factor, and albumin were studied.

Sixteen adverse reactions occurred in 15 patients; the reactions affected the liver (six patients), the lung (three), the skin (three), the bone marrow (three), and the oral mucosa (one). They recovered after methotrexate was discontinued or reduced, without steroid treatment. Thirty of these 15 patients showed a trend (SD decrease in

---

**Table 1**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Antiphospholipid Antibodies</th>
<th>Active Disease</th>
<th>Prolonged Steroid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

**Table 2**

<table>
<thead>
<tr>
<th>Immunoglobulin Levels</th>
<th>Lymphocyte Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>IgA</td>
</tr>
<tr>
<td>17.99</td>
<td>5.14</td>
</tr>
<tr>
<td>10.15</td>
<td>3.69</td>
</tr>
<tr>
<td>16.75</td>
<td>4.33</td>
</tr>
</tbody>
</table>
Comparison of patients with and without adverse reactions.

Table 1 Pretreatment value, decrease, decrease ratio, and threshold value of immunoglobulin levels and lymphocyte count in patients used to differentiate between patients with and without adverse reactions. Values are shown as mean (SD)

<table>
<thead>
<tr>
<th></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>IgG (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>20.87 (7.34)(15)</td>
<td>20.12 (5.50)(83)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−6.23 (3.53)(15)</td>
<td>−1.47 (3.73)(81)</td>
<td>***</td>
<td>4.62</td>
<td>***</td>
</tr>
<tr>
<td>(Post−pre)/pre</td>
<td>−0.30 (0.13)(15)</td>
<td>−0.06 (0.10)(81)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA† (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>4.50 (2.17)(15)</td>
<td>4.13 (1.61)(93)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−1.35 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>***</td>
<td>0.83</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>***</td>
<td>0.189</td>
<td>***</td>
</tr>
<tr>
<td>IgM‡ (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.03 (0.86)(15)</td>
<td>2.04 (0.84)(83)</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Post−pre (g/l)</td>
<td>−0.77 (0.60)(15)</td>
<td>−0.15 (0.44)(81)</td>
<td>***</td>
<td>0.26</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>***</td>
<td>0.257</td>
<td>***</td>
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<tr>
<td>γ Globulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>15.64 (7.00)(13)</td>
<td>15.54 (4.69)(74)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−5.07 (3.61)(12)</td>
<td>−1.30 (3.22)(67)</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)(67)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1.82 (0.80)(15)</td>
<td>1.38 (0.61)(81)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (10³/l)</td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.50)(80)</td>
<td>***</td>
<td>0.18</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>*</td>
<td>0.267</td>
<td>***</td>
</tr>
</tbody>
</table>

NS = p>0.05; *p<0.05; ***p<0.005; ****p<0.0001.

‡To differentiate between patients with and without adverse reactions.

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 eosinophil count decreased in responders and in patients without adverse reactions, whereas the ejection of steroid treatment was not compared with pretreatment values. The reductions and reduction ratios compared 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. 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 compared 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 78 responders. 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. Immunosuppression 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 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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A "missed" cryoglobulin: the importance of in vitro calcium concentration

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