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 program—has the best chances of success, although even rheumatologists can practise amateur cognitive behavioural therapy in the clinic’. Is Dr Reilly really suggesting that a rheumatologist, with his amateur efforts, can achieve 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.2 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 such programmes in the USA is well recorded.3 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.4

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 their problem alone, shouldn’t his effective course 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?

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 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. High quality research has a longer shelf life than eight years.

P A REILLY

Frimley Park Hospital, Frimley, Camberley, Surrey GU16 5UJ, UK

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.1 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 were either undetectable or found at very low levels it was several years despite repeated careful blood sample examination 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 concentrations.

Case report

A 52 year old man with multiple lipoma 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. He was diagnosed with coeliac 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 1.2–2.7). Non-rheumatoid factors, including the Rose-Waaler test (Sanoht Pasteur, Marnes La Coquette, France), were positive (table 1), but other serum autoantibodies remained negative, including antinuclear, and DNA and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C4 <0.06 g/l (normal range 0.10–0.40; Behring Dade, Deerfield, USA) 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 serology markers was 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, 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 skin flare up occurred in August 1998, 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 fibrinous 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 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...
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) 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>0.10</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></td>
<td>1/128</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>0.10</td>
</tr>
<tr>
<td>November 1998</td>
<td>1105†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>0.09</td>
</tr>
<tr>
<td>December 1998</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>0.10</td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td>ND</td>
<td>0.10</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>0.10</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>0.10</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 antis IgG, IgA, IgM, κ and λ chains labelled with alkaline phosphatase on cryoglobulin obtained with conventional assay (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).

polyclonal rheumatoid factors are nearly always part of mixed cryoglobulins, where they bind to immune complexes—principally antigen complexed IgG—that subsequently precipitate.8,10 Nevertheless, when using conven- tional 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 cryo- globulin related kidney complications prompted us to perform further tests for cryo- globulins, including the method described above. Then, a high titre type II cryoglobulin (>1000 µg/ml) was isolated, and subse- quently 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 mono- clonal IgM in the cryoprecipitate, and allowed identification of an additional mono- clonal 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, indicat- ing 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.8,9,10 Firstly, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondly, the large immune com- plexes 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.7 This property might account for some of the discrepancies observed between the conventional and the current assay. It might also explain the sever- ity of the symptoms in vivo. Further investi- gation is needed to approach the other deter- minant 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.11
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 large centres.

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 of f 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 in postmenopausal women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria were enrolled. 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 lumbar spine 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 2x2 table was used to evaluate the positive and negative predictive values 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). CDA 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 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.

Correspondence to: Dr Nolla

J M NOLLA
C GÓMEZ-VAQUERO
D ROIG-ESCOFET
Rheumatology Service (P1 10–2), Cusat Santitaria I Universitària de Bellvitge, Feixa Llarga s/n, 08907 L’Hospital, Barcelona, Spain

Correspondence to: Dr Aumaitre

JEAN-DANIEL TISSOT
Fondation Centre de Transfusion Sanguine (SRTS VD), 27 rue du Bugnon, CH-1005 Lausanne, Switzerland

Correspondence to: Dr Aumaitre

HAKIM MAHAMEDI
OLIVIER AUMAITRE
Department of Internal Medicine, Gabriel Montpellier Hospital, CHU of Clermont-Ferrand, BP 69, 63003 Clermont-Ferrand Cedex 1, France

ARLETTE TRIDON
Laboratory of Immunology, University of Clermont-Ferrand and Pharmacy, BP 38, 63001 Clermont-Ferrand Cedex 1, France

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>Age (y)</th>
<th>61.2 (8.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of postmenopausal period (y)</td>
<td>13.3 (7.5)</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis (y)</td>
<td>9.7 (6.4)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (n)</td>
<td>32</td>
</tr>
<tr>
<td>Erosive RA (n)</td>
<td>16</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>16</td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
<td>0.840 (0.150)</td>
</tr>
<tr>
<td>BMD at the femoral neck (g/cm²)</td>
<td>0.560 (0.110)</td>
</tr>
<tr>
<td>BMD at the middle phalanx of the third finger (g/cm²)</td>
<td>0.390 (0.090)</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 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 patient was otherwise asymptomatic. 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 transaminase (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 h. The serum ferritin was higher than 1500 µg/l (normal value: 20–250 µg/l). Roentgenogram of chest and abdominal CT scans 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. Immunological studies in five patients with adult onset Still's disease showed no 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. 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 individuals. Echovirus 7, murmumps, cytomegalovirus, para-influenza, Epstein-Barr virus, influenza A, parvovirus B19, hepatitis B or C and rubella virus 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 eight 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.

FRANCISCO JAVIER ESCUDERO OLEGAR CENIC FALCÓ TOMAS FERNÁNDEZ DE SEVILLA Service of Internal Medicine, Hospital General Universitario Vall d’Hebron Barcelona, Spain AGUSTÍ SELLAS Service of Rheumatology, Hospital General Universitario Vall d’Hebron Correspondence to: Escudero, C/ Amapolas, 37 2ª Esc 1º 2ª, 08906 L’Hospitalet de Llobregat, Spain


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 vasoactive smooth muscle cells. 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 pathological control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure by relaxing the cardiovascular system. 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 chemo-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, myocutaneous, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc. In the 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 without or with 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 measured by echocardiogram. In the three patients with PH the pressures of the pulmonary artery pressures of patients 4, 5, and 6 were 46, 59, and 60 mmHg, respectively. Levels of adrenomedullin in the plasma of patients 4, 5, and 6 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 of patients with SSc with PH were significantly higher in patients with SSc with PH than in healthy volunteers (p = 0.011). We recently obtained similar results when comparing adrenomedullin concentrations in patients with SSc with PH and those with SSc without PH (p = 0.001). The concentrations of adrenomedullin in the plasma of patients with SSc with PH were higher in patients with SSc with PH than in healthy volunteers (p = 0.011).

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). The concentrations of adrenomedullin in the plasma of patients with SSc with PH were raised compared with those in patients with SSc without PH (p = 0.011) (fig 1A). 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, 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.

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 (women and 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 all 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 = 0.41) (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, 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.

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vertebral body involvement by APLS is AVN involving an isolated L2 vertebral body. The first is the atypical presentation of the development of AVN at an atypical site. SLE with secondary APLS who had been hyperlipidaemia. all along been normotensive and she has no much improved after the operation. Her back pain was fusion. Histological examination of the indicated surgery unit for a L1 to L3 vertebral spine with increase in signal over the L2 vertebral bodies in 1994. Bone marrow necrosis associated with an- tiphospholipid antibody syndrome presenting with multiple thromboses and sites of avascular necrosis. J Rheumatol 1994;21:2376–9.

Figure 1 Plain radiograph of the lumbosacral spine (AP view) of the patient.

Figure 2 T2 weighted magnetic resonance scan sagittal image of the lumbosacral spine of the patient.

**Immunoglobulin and lymphocyte decrease concurrent with adverse reactions induced by methotrexate for RA**

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, 1.00, 3.66 g/l; and lymphocyte ratio, 0.42, 1.56×10^9/l, respectively. We then investigat- ed whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate treated RA 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, was defined by a decrease in swelling and pain of more than two joints, a decrease of >20 mg/l in the C reactive protein (CRP) level, adverse reac- tions, 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 metho- trexate was discontinued or reduced, without steroid treatment. Thirty of these 15 patients showed a mean (SD) decrease in

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>
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<tbody>
<tr>
<td>IgG†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>20.87 (7.34)(15)</td>
<td>20.12 (5.50)(83)</td>
<td>NS</td>
<td></td>
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</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>IgA†</td>
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<td></td>
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<tr>
<td>Pre</td>
<td>4.50 (2.17)(15)</td>
<td>4.13 (1.61)(83)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post−pre (g/l)</td>
<td>−1.15 (0.87)(15)</td>
<td>−0.21 (0.65)(81)</td>
<td>****</td>
<td>0.83</td>
<td>***</td>
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<tr>
<td>IgM†</td>
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<tr>
<td>Pre</td>
<td>2.03 (0.86)(15)</td>
<td>2.04 (0.84)(83)</td>
<td>NS</td>
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<tr>
<td>Post−pre (g/l)</td>
<td>−0.37 (0.60)(15)</td>
<td>−0.15 (0.44)(81)</td>
<td>****</td>
<td>0.26</td>
<td>***</td>
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<tr>
<td>γ Globulin</td>
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</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>****</td>
<td>2.34</td>
<td>***</td>
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<tr>
<td>Lymphocyte</td>
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</tr>
<tr>
<td>Pre</td>
<td>1.82 (0.80)(15)</td>
<td>1.38 (0.61)(81)</td>
<td>*</td>
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<tr>
<td>Post−pre (10^9/l)</td>
<td>−0.6 (0.55)(14)</td>
<td>−0.01 (0.58)(80)</td>
<td>****</td>
<td>0.18</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.

The authors thank Dr Victoria Elegant and Ms Keiko Miyahara for their help.

SHIGEKO INOKUMA
HAJIME KONO
HISANORI NAKAYAMA
JUNKO YAMAZAKI
Department of Allergy and Immunological Diseases,
Tokyo Metropolitan Komagome Hospital,
Tokyo, Japan

Email: inokuma-ki@komagome-hospital.bunkyo.tokyo.jp

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ROBINA LLOYD

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