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 a cognitive behavioural therapy is set 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.

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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.1 To ensure optimal detection, cryoglobulin 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 several years after 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 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 of the lower legs and 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. Gammaglobulins 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 1.09–3.29) with a positive rheumatoid factors, including the Rose-Waaler test (Sanofi Pasteur, Marnes La Coquette, France), were positive (table 1), but other serum autoantibodies remained negative, including antinuclear, anti-DNA, and antineutrophil cytoplasmic antibodies. Complement concentrations were notably down, both for C4 <0.06 g/l (normal range 0.10–0.46; Behring Diagnostics, 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 sero markers was negative for A, B and C viruses. Cryoglobulin measurements were initially negative or inconclusive (table 1). Proteinaemia 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 flare up occurred in August 1998 with source, including 3 g daily proteinaemia of recent onset. The urinary sediment contained 20 red cells per high power field. Renal biopsy showed endocapillary proliferative glomerulonephritis with glomerular crescents and capillary 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, proteinaemia 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 pro- toms persisted and renal complications worsened, with a raised proteinaemia 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
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).

The precipitated protein was isolated on a Protein G-Sepharose column. Solubility of the cryoprecipitate was measured by adding HCl-glycine, pH 2.2, and analysed with two dimensional polyacrylamide gel electrophoresis. The influence of calcium concentration on cryoprecipitability was investigated as follows. Solubility of the cryoglobulin obtained with distilled water was measured by adding Hanks's solution containing 1.26 mM Ca²⁺, or 0.80 mM Mg²⁺, or both. The dissolved proteins were measured as described above. The solubility 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 IgM was sometimes found on immunofluorescence 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 IgM 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 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 polyclonal IgG, with only traces of the monoclonal IgMs, 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. Firstly, 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 support 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.
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.

Correspondence to: Dr Aumaître

**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 (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.2 (9.3)</td>
</tr>
<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>16</td>
</tr>
<tr>
<td>Erosive RA (n)</td>
<td>32</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>32</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.*

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 specialized clinics.

Computed digital absorptiometry (CDA) of the hand is a new bone densitometry technique, designed to assess the BMD of the middle phalanges 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 all risk factors, and to monitor the response to therapeutic intervention has not been established.

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

We have undertaken a study to evaluate whether CDA might be a useful screening technique for identifying the patients with RA who should be examined by DXA. Over a period of three months all postmenopausal women with RA, evaluated in the rheumatology outpatient clinic, who fulfilled the inclusion criteria and consent was obtained from 40 of them. 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 at the lumbar spine and the non-dominant hand correlated significantly (r = 0.51, p<0.01). Similarly, BMD at the femoral neck and at the non-dominant hand were significantly correlated (r = 0.51, p<0.01). DXA showed that 13 patients had osteoporosis and CDA that 16 patients had the disease in at least one of the evaluated zones. The positive predictive value of CDA for the diagnosis of osteoporosis was 56%. The negative predictive value for the diagnosis of osteoporosis was 83%.

The correlations found between BMD at the non-dominant hand and at the lumbar spine and femoral neck were moderate. A negative predictive value of 0.51 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
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 purpuric rash, myalgia, sore throat and headache. At the time of admission the temperature was 40°C and the pulse rate 104 beat/min. The rash consisted of small purpuric macules over back, periorbicular, legs and arms. The patient was afebrile and afebrile. Some small cervical lymphadenopathies were detected. The leucocyte count was 42.3 × 10^9/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 h. The serum ferritin was higher than 1500 µg/l (normal value 20–250 µg/l). Roentgenogram of chest and electrocardiogram 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 burneti, Chlamydia and Rickettsia were negative. A seroconversion in the rubella IgG antibody titre was 140 000 IU/l.

Rickettsia conorii were negative. The initial titre was 1:40 and raised also in the plasma of patients with adult onset Still's disease. In 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 as 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, OSCAR LEN
VIVENC FALCÓ

Matter arising, Letters

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 and has 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 immune 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, protecting the cardiovascular system. Furthermore, adrenomedullin regulates not only vascular tonic but also vascular function through the autocrine/paracrine system, stimulating Ca^2+ accumulation in a dose-dependent manner, and exerting an anti-inflammatory effect by inhibiting the production of a chemotactic attractant from alveolar macrophages.

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

We obtained plasma from three women with SSc with PH (aged 43–72), 10 patients with SSc without PH (nine women, one man, aged 22–60), and one female patient with primary PH. The diagnosis of SSc was based on accepted criteria. We diagnosed PH in...
patients with SSc whose right ventricular systolic pressure was higher than 25 mm Hg measured by echocardiogram. In the three patients with SSc with PH we confirmed PH by catheterisation. The pressures of the pulmonary artery of these three patients were 45, 51, and 54 mm Hg, respectively. All patients with SSc had diffuse-type SSC without interstitial pneumonia, which was diagnosed as interstitial fibrosis by computed tomography. The three patients with PH were taking the following drugs: 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 with PH had diffuse-type SSC. Six normal volunteers (three women and three men, age 29–40) were also studied. Concentrations of adrenomedullin were measured by radioimmunoassay. Statistical significance was analysed with the Mann-Whitney U test.

Concentrations of adrenomedullin in the plasma were significantly higher in patients with SSc with PH than in those with SSc without PH (p = 0.011) or than in normal volunteers (p = 0.020) (fig 1A). The concentrations of adrenomedullin or endothelin-1 in the plasma from a patient with PH was 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 inhibit either the spasm of pulmonary vessels or the proliferation of endothelial cells of the vessels, though the levels of adrenomedullin in plasma increased enough to antagonise the effects of endothelin-1 in patients with SSc. It has been recently reported that chronic infusion of adrenomedullin reduces PH and right ventricular hypertrophy in rats. 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.

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, 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.

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 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 from 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 the oral prednisolone dose was gradually brought down to 10 mg daily. She was also given dipipyramide, an anti-platelet agent, and atenolol for hypertension that was introduced 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 lumbosacral spine. Figure 2 shows the T2 weighted magnetic resonance sagittal image of the lumbosacral spine of the patient. 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 occurring in the hip, it is commonly seen in elderly patients after fracture neck of femur, as a result of disturbance to its blood supply. Previous studies in patients with SLE have suggested high dose and prolonged use of corticosteroids causes AVN. Active disease and the presence of APL antibodies may also have important roles in the development of AVN in these patients. It is interesting that our patient had features of secondary APLS 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, or all three, led to AVN remains unresolved. The 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 PaO₂ was 57 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, 1.36 g/l; and lymphocyte count 1.96, 1.06, 1.36×10^9/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, was defined as 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 reactions, lymphocyte and eosinophil counts, serum concentrations of immunoglobulins, fraction, rheumatoid factor, and albumin were studied. Sixteen adverse reactions occurred in 15 patients; the reaction affected the lungs (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. Thirteen of these 15 patients showed a trend (SD) decrease in

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

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

In 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. 1,2 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 PaO₂ was 57 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, 1.36 g/l; and lymphocyte count 1.96, 1.06, 1.36×10^9/l, respectively. We then investigated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate treatment develop.

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