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 [2]. Is Dr Reilly really suggesting that a rheumatologist’s amateur efforts offer the best outcome for people with fibromyalgia?

Dr Reilly offers no evidence to support this statement. He does, however, find evidence to raise questions as to the value of patient self help groups. Dr Reilly cites a 1992 paper that reports an association between membership of such a group and worse prognosis in chronic fatigue syndrome. [3] As the authors emphasised the caution with which the results should be interpreted, it is surprising that Dr Reilly has used this evidence to inform his clinical practice.

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

Challenging Arthritis is a self management programme—and that title was chosen very deliberately. It is run by people with arthritis for people with arthritis. It gives people the skills to take control of their lives and their arthritis. It is practical and positive, and it works. The effectiveness of similar programmes in the USA is well recorded. [4]

Experience in the United Kingdom shows similar results, including better understanding of symptoms, improved communication with medical staff, and increased use of exercise and relaxation techniques. Probably most importantly of all, self management programmes significantly decrease pain, fatigue, and anxiety. [5]

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

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

Given Dr Reilly’s desire to disabuse patients of the notion that their fibromyalgia is his problem alone, shouldn’t his treatment, even if it is run by a patient self management training for people with arthritis. Psychological Health 1998;3:387–93.

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 consequences. 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 cryoglobulinemia may manifest clinically as skin, articular, renal, and peripheral nerve complications. [6] To ensure optimal detection, cryoglobulin concentration must be obtained and preserved at 37 °C. We report on a patient whose clinical presentation was suggestive of cryoglobulinemia. Because cryoglobulins had been either undetectable or found at very low levels 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, 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 [7-9]. 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 1.07–6.15). Apart from rheumatoid factors, including the Rose-Waaler test (Sanoft Pasteur, Marnes La Coquette, France), were positive (table 1), but other serum autoantibodies remained negative, including antinuclear, anti-double stranded 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 0.10–0.80). A complete set of serum 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, plasma pheresis 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 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 capillary loop fibrinous thrombi (no glomerulus on the sample for immunofluorescence study). The patient temporarily improved with plasmapheresis and methylprednisolone pulses followed by high oral prednisone (50 mg/day). From September 1998 to January 1999, proteinuria increased to 5.4 g/day, and a high serum cryoglobulin concentration was then first detected with the assay described below (table 1). Azathioprine was replaced by monthly intravenous cyclophosphamide (1 g per infusion), associated with subsequent plasmapheresis in January and April 1999. Despite this treatment the patient’s symptoms persisted and renal complications worsened, with a raised proteinuria at 6.28 g/day and a serum creatinine at 192 μmol/l in July 1999. A new evaluation was made. A bone marrow biopsy was normal. The skin biopsy showed leuкоagocytoclastic vasculitis with slight


1 The authors


1 The authors


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

<table>
<thead>
<tr>
<th>Date</th>
<th>Cryoglobulinaemia (µg/ml) *</th>
<th>Type</th>
<th>Rheumatoid factor (Rose-Waaler test)</th>
<th>C4 (g/l)</th>
<th>CH50 (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 1994</td>
<td>29</td>
<td>Oligoclonal IgM</td>
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<td>0</td>
<td>&lt;0.06</td>
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<tr>
<td>June 1996</td>
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<td>Oligoclonal IgM</td>
<td></td>
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<td>&lt;0.06</td>
</tr>
<tr>
<td>August 1996</td>
<td>17</td>
<td>Oligoclonal IgM</td>
<td></td>
<td>ND</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>December 1996</td>
<td>188</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>March 1997</td>
<td>4</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1 / 128</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>October 1998</td>
<td>63</td>
<td>III, polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>0.10</td>
</tr>
<tr>
<td>November 1998</td>
<td>110†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>December 1998</td>
<td>166†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>January 1999</td>
<td>1660†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>February 1999</td>
<td>1031†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>0.08</td>
</tr>
<tr>
<td>March 1999</td>
<td>1000†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>ND</td>
</tr>
<tr>
<td>April 1999</td>
<td>273† (after plasmapheresis)</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>1/128</td>
<td>0.99</td>
</tr>
<tr>
<td>May 1999</td>
<td>848†</td>
<td>II, IgMx + polyclonal IgG, IgA, and IgM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

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

Oligoclonal IgM deposits were obtained and centrifuged at 37°C for eight days. The precipitate was lost in the PBS. Then, each precipitate was washed with hypotonic serum, though they lead to the isolation of protein G columns and monoclonal 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 IgM. Finally, electrophoretic studies of the proteins eluted from protein G columns showed the presence of polyclonal IgG, with only traces of the monoclonal IgM, 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. 5–7 First, rheumatoid factors bind to immune complexes at reduced temperature because of a cold enhanced affinity. Secondly, the large immune complexes precipitate. This requires favourable physicochemical conditions, including suitable pH and ionic strength of the solvent. Usually, the precipitate is stable in saline. Our data suggest that calcium concentration may be crucial for cryoglobulin precipitation, as in the case reported by Qi et al. This property might account for some of the discrepancies observed between the conventional and the current assay. It might also explain the severity of the symptoms in vivo. Further investigation is needed to approach the other 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. 11
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 cryoglobulin can include dependence upon calcium concentration, should be looked for in such circumstances.

We thank Ray Langford for reviewing the English manuscript.


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>Mean (SD)</th>
</tr>
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<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 (%)</td>
<td>0.9 (0.6)</td>
</tr>
<tr>
<td>Erosove RA (%)</td>
<td>0.840 (0.150)</td>
</tr>
<tr>
<td>Treatment with low dose glucocorticoids (n)</td>
<td>0.460 (0.110)</td>
</tr>
<tr>
<td>BMD at the lumbar spine (g/cm²)</td>
<td>0.390 (0.090)</td>
</tr>
</tbody>
</table>

BMD = bone mineral density.

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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 emphasis 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 admission 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 pyrexemia. Some small cervical lymphadenopathies 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 bone density analysis were normal as well as blood and urine cultures. Abdominal computed tomography showed hepatosplenomegaly. An electromyographic study was normal. Tests for antinuclear antibodies and rheumatoid factor were negative. Serum concentrations of immunoglobulins and complement were normal. Serological tests for hepatitis A, B or C, cytomegalovirus, parvovirus B19, human immunodeficiency virus 1 and 2, Epstein–Barr virus, Mycoplasma, Treponema pallidum, Borrelia burgdorferi, Toxoplasma, Salmonella, Brucella, Legionella, Coxiella burnetti, Chlamydia and Rhinitis were all 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 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 in this way 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 has been supported by the increase in IgG antibody titre without increase in IgM concentration. A seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other measured antibody titres.

Although aetiology of adult onset Still’s disease is unknown, some authors have tried to demonstrate that infective agents, especially viruses, can be the trigger of the illness in susceptible patients. Parovirus, echovirus 7, mumps, cytomegalovirus, influenza A, parvovirus B19, hepatitis B or C and rubella have been associated. The relation between rubella virus and adult onset Still’s disease has been reported in some cases and series reports since the initial description by Bywaters in 1971. Wouters et al performed exhaustive virological studies in patients with adult onset Still’s disease in an early phase of the illness and found evidence of viral infection in three cases, two of them corresponding to rubella. The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still’s disease.

In summary, we think that the increased rubella IgG antibody titre in our patient should not be considered an anecdotal event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports, supports the hypothesis about the role of viruses in the aetopathogenesis of adult onset Still’s disease.

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VICENC FALCO

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Adrenal medullin is a hypotensive peptide newly found in human pheochromocytoma tissue. The peptide comprises 52 amino acids with an intramolecular disulphide bond. The mRNA of adrenomedullin has been detected in endothelial cells, vascular smooth muscle cells and alveolar macrophages. Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasoactive effect, antagonising the vaso- petic 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 and, thereby, protecting the cardiovascular system. Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating the adrenomedullin formation in the endothelial cells. In this way, adrenomedullin shows a beneficial manner, and exerting an anti-inflammatory effect by inhibiting the production of a chemotactic chemoattractant 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 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, with or without PH, to elucidate the role of adrenomedullin in the pathogenesis of SSc.

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 diastolic pulmonary artery pressures of patients 4, 5, and 6 were 46, 59, and 60 mmHg, respectively. The pressures of 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.

Patients 4, 5, and 6 were taking the following drugs: nifedipine hydrochloride (patient 1), nifedipine and triclopidine hydrochloride (patient 2), and nifedipine and triclopidine hydrochloride and methylprednisolone (patient 3). For the comparison group we selected patients with diffuse-type SSC without PH, as all of these 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 assessed by 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 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 we measured plasma adrenomedullin concentrations in patients with Raynaud’s phenomenon. J Rheumatol 1999;26:759–60.


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. She was pregnant 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 the oral prednisolone dose was gradually brought down to 10 mg daily. She was also given dipipridamole, an anti-platelet agent, and atenolol for hypertension that was diagnosed during subsequent follow up but there was no other evidence of renal involvement. Calcium supplements and vitamin D were started for prophylaxis against osteoporosis. She had another flare of her SLE in October 1988 when she presented with polyarthralgia and significant thrombocytopenia. Her warfarin was stopped in view of the potential increase risk in bleeding tendency. Her prednisolone was increased to 40 mg daily to no avail. Splenectomy was performed, after which her platelet count stabilised. She had an unsuccessful pregnancy with intrauterine death in the same year. Her disease was better controlled with prednisolone (5-10 mg/day) and azathioprine until April 1998 when she complained of constant and severe back pain, which was aggravated by movement. A plain radiograph showed no obvious abnormality but magnetic resonance imaging of the thoracolumbar spine showed features suggestive of bone infarction of the L2 vertebral body. Bone scan did not pick up any other site of involvement by AVN. Figure 1 shows the plain radiograph of the lumbar spine. Figure 2 shows the T2 weighted magnetic resonance sagittal image of the thoracolumbar spine with increase in signal over the L2 vertebral body. It was referred to the orthopaedic surgery unit for a L1 to L3 vertebral fusion. Histological examination of the involved site showed bone necrosis and features compatible with AVN. Her back pain was much improved after the operation. She has all along been normotensive and she has no hyperlipidaemia.

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

This case highlights two interesting points. The first is the atypical presentation of the development of AVN at an atypical site. The second is the diagnosis of AVN involving an isolated L2 vertebral body. Vertebral body involvement by APLS is seldom reported. Egan et al reported on a patient with catastrophic APLS who presented with the onset of AVN involving multiple sites including T8, L4 and L5 vertebral bodies in 1994. Bone marrow necrosis without bony destruction has also been reported to be associated with APLS, usually in the context of catastrophic APLS and picked up by bone scan as multiple hot spots. The lunate bone is another unusual site of involvement by AVN. Kienbock’s disease (AVN of lunate bone) was reported in a patient with primary APLS and two others with antiphospholipid (APL) antibodies but without other clinical features that satisfied the diagnosis of APLS.

Secondly, the pathogenesis of 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 of her L2 vertebral body is unclear. In view of this, we have recently performed a case-control study to evaluate the role of each of these individual potential risk factors.

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

Figure 2 T2 weighted magnetic resonance scan sagittal image of the lumbar sacral 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 1.10×10⁹/l and PaO₂ 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, 1.04, 2.36 g/l, and albumin 3.53, 0.42, 1.56×10⁹/l, respectively. We then investigated whether immunoglobulin levels and lymphocyte count decrease when adverse reactions to methotrexate 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 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 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 16 patients showed a mean (SD) decrease in
Comparison of patients with and without adverse reactions. Normal range for IgG is 8.71–20.7 g/l, IgA 0.12–5.80 g/l, and IgM 0.53–2.98 g/l. NS = p<0.05; *p<0.05; ***p<0.005; ****p<0.0001. 78 responders. The greater decreases in reduction was seen in lymphocyte counts, in immunoglobulins and reductions 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).

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 (%)</th>
<th>Without adverse reaction (%)</th>
<th>p Value‡</th>
<th>Threshold value</th>
<th>p Value¶</th>
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</thead>
<tbody>
<tr>
<td>IgG</td>
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<tr>
<td>Pre</td>
<td>20.87 (7.34)</td>
<td>20.12 (5.50)</td>
<td>NS</td>
<td>4.62</td>
<td>***</td>
</tr>
<tr>
<td>Post–pre (g/l)</td>
<td>−6.23 (3.53)</td>
<td>−1.47 (3.73)</td>
<td>***</td>
<td>0.171</td>
<td>***</td>
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<tr>
<td>IgA</td>
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<tr>
<td>Pre</td>
<td>4.50 (2.17)</td>
<td>4.13 (1.61)</td>
<td>NS</td>
<td>0.83</td>
<td>***</td>
</tr>
<tr>
<td>Post–pre (g/l)</td>
<td>−0.35 (0.87)</td>
<td>−0.21 (0.65)</td>
<td>***</td>
<td>0.189</td>
<td>***</td>
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<tr>
<td>IgM</td>
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<tr>
<td>Pre</td>
<td>2.03 (0.86)</td>
<td>2.04 (0.84)</td>
<td>NS</td>
<td>0.26</td>
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</tr>
<tr>
<td>Post–pre (g/l)</td>
<td>−0.35 (0.10)</td>
<td>−0.07 (0.17)</td>
<td>***</td>
<td>0.257</td>
<td>***</td>
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<td>γ Globulin</td>
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<tr>
<td>Pre</td>
<td>15.64 (7.00)</td>
<td>15.54 (4.69)</td>
<td>NS</td>
<td>2.38</td>
<td>***</td>
</tr>
<tr>
<td>Post–pre (g/l)</td>
<td>−0.77 (0.60)</td>
<td>−0.15 (0.44)</td>
<td>***</td>
<td>0.243</td>
<td>***</td>
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<td>Lymphocyte</td>
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<tr>
<td>Pre</td>
<td>1.82 (0.80)</td>
<td>1.38 (0.61)</td>
<td>*</td>
<td>0.18</td>
<td>***</td>
</tr>
<tr>
<td>Post–pre (10⁹/l)</td>
<td>−0.6 (0.55)</td>
<td>−0.01 (0.58)</td>
<td>***</td>
<td>0.267</td>
<td>***</td>
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<tr>
<td>(Post–pre)/pre</td>
<td>−0.35 (0.31)</td>
<td>0.12 (0.71)</td>
<td>***</td>
<td>0.15</td>
<td>***</td>
</tr>
</tbody>
</table>

NS = p<0.05; *p<0.05; ***p<0.005; ****p<0.0001.
‡Comparison of patients with and without adverse reactions.
¶To differentiate between patients with and without adverse reactions.