PostScript

MATTERS ARISING

Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled "Antiphospholipid antibodies and RA: presence of β2GPI independent aCL" by Bonnet et al published in the *Annals* in March 2001.1 We believe that the letter needs additional clarification owing to inconsistencies in the terminology, methodology of antiphospholipid antibody (aPL) detection, and determination of positive values.

The use of the term "anticardiolipin antibodies" was somewhat misleading. The term was introduced and abbreviated as "aCL," a group of antibodies detected in many conditions, but the β2 glycoprotein I (β2GPI) dependence of the aCL was not defined, even though the authors focused on β2GPI independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines the antibodies detected by the classical aCL enzyme-linked immunosorbent assay (ELISA).2—That is, both β2GPI dependent and β2GPI independent antibodies.

There were some potential methodological errors in determining β2GPI independent aCL. It was shown that antibodies against β2GPI (anti-β2GPI) from patients with the antiphospholipid syndrome (APS) have the ability to bind β2GPI in complexes with cardiolipin only if the β2GPI concentration in solution is high enough. The threshold concentration of β2GPI was found to be just about 2 µg/mL, because no binding of anti-β2GPI was seen when serum samples were diluted 1:200 or more.2 As the physiological concentration of β2GPI in human serum is approximately 200 µg/mL, the threshold binding concentration is reached at a serum dilution of 1:100. In the presence of a relatively high concentration of endogenous β2GPI, the statement that antibodies detected by this method are exclusively β2GPI independent is unjustified, as the sera containing high titres of anti-β2GPI might have yielded positive results by the method described in the letter.

The definition of antibody units in the letter is not clear and using Harris’s standards for β2GPI independent aCL is not appropriate. With the use of Harris’s standards,3 the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined.4 However, Harris’s standards were designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominately, β2GPI dependent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standards for β2GPI independent assays. The interpretation of anti-β2GPI ELISA as a method to detect β2GPI dependent aCL may not be valid in all cases. It was shown that not all anti-β2GPI binding β2GPI adsorbed on polystyrene high binding plates also recognize β2GPI associated with cardiolipin. We reported this binding pattern for anti-β2GPI in children with atopic dermatitis,5 and the same was shown also for some patients with autoimmune diseases, including APS.6

The method for purification of β2GPI was not described. Because the authors focused on patients with rheumatoid arthritis (RA), it should be ensured that immunoglobulins were specifically removed from the β2GPI preparation. If this purification step was not carried out, traces of immunoglobulins in the β2GPI preparation might have yielded positive results for sera containing high titres of rheumatoid factor (RF). In fact, all sera containing IgM anti-β2GPI also had RF and the authors already suspected that this might be due to non-specific binding involving RF.

The method for determining cut off values was not explained and the number of normal human sera (NHS) included in the study as negative controls was not given. From the data presented in the letter, one may conclude that the cut off values were arbitrarily set at 20 units both for IgG and IgM isotypes of β2GPI independent aCL and for anti-β2GPI. We recently compared the sensitivity of anti-β2GPI ELISA and classical aCL ELISA. The results showed great differences between their sensitivities and therefore also between the cut off values calibrated by the same standards.6 In addition, the authors did not report the proportion of NHS positive for each assay and the values of positive samples compared with patients with RA. Instead, they just referred to one study,7 which is only one of the several published estimations of aPL in healthy subjects.

We would like to support our criticism by adding some data about aPL in our patients with RA. We randomly selected 53 serum samples from patients fulfilling the ARA criteria for RA and 53 NHS as negative controls. The samples were tested for anti-β2GPI, β2GPI dependent aCL, and β2GPI independent aCL. The cut off values for anti-β2GPI were set as described8 by calculating the mean ± 2 SD of logarithms of absorbance values for NHS and the 95th centile value of 32 NHS for both β2GPI dependent and β2GPI independent aCL. For the anti-β2GPI determination, we used affinity purified β2GPI adsorbed on Costar high binding plates as previously described.9 The β2GPI preparation did not contain any immunoglobulins. β2GPI independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for β2GPI dependent aCL on the same plate by adding β2GPI in parallel duplicate wells. The final concentration of β2GPI was 10 µg/mL. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β2GPI. For the final determination of β2GPI dependent binding, the values obtained in wells without β2GPI were subtracted from the values measured in wells with added β2GPI. The patients’ histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the χ2 test where appropriate.

Table 1 presents the frequency of positive sera in each group (NHS, RA, RA-RF positive, and RA-RF negative). The frequency of increased anti-β2GPI, β2GPI dependent aCL, and β2GPI independent aCL was higher in patients with RA than in controls, but the difference was significant only for anti-β2GPI. There were no differences in the frequency of

### Table 1: Frequency of anti-β2GPI, β2GPI dependent aCL, and β2GPI independent aCL in patients with rheumatoid arthritis (positive or negative for RF) and normal controls

<table>
<thead>
<tr>
<th>No of positive samples:</th>
<th>Anti-β2GPI</th>
<th>β2GPI dependent aCL</th>
<th>β2GPI independent aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgA</td>
</tr>
<tr>
<td>NHS (n=32)</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RA (n=33)</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>RA-RF (n=36)</td>
<td>6</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>RA-RF ~ (n=17)</td>
<td>16</td>
<td>22</td>
<td>32</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; β2GPI, β2 glycoprotein I; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.

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any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2-GP1 and anti-β2-GP1 dependent aCL of IgA isotype. Interestingly, 5/11 RA sera which showed binding to β2-GP1 adsorbed on a high binding plate did not recognise β2-GP1 associated with cardiolipin, as already reported. In contrast, 3/9 RA sera binding β2-GP1 complexed with cardiolipin did not recognise β2-GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2-GP1 in RA, which may differ in fine specificity from anti-β2-GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β2-GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β2-GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2-GP1 (10 μg/ml) lowered the binding of β2-GP1 independent aCL by about 50%, most probably owing to the competition between β2-GP1 independent aCL and β2-GP1 for the same binding sites on cardiolipin. RA patients with RA may have anti-β2-GP1 and β2-GP1 dependent aCL, which might be associated with the signs of APS. The importance of distinguishing β2-GP1 independent aCL has not been fully clarified. It seems that the presence of independent aCL do not confer an increased risk for APS in RA.

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References
5 Harris EN. Special report. The second international antiphospholipid standardization working party the Kongreß der antiphospholipid antibody study (KAPS) group. Am J Clin Pathol 1990;94:476–84.

Authors' reply
In response to the comments of Ambrozic et al we would like to make some clarification to the data published earlier in the Annals.

The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera. We found that the dependence of aCL on β2-glycoprotein 1 (β2-GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2-GP1 in blocking buffer (containing fetal calf sera or bovine serum albumin). In our study, the blocking solution did not contain bovine or calf sera but only purified bovine serum albumin. So, this method was adapted to detect antibodies directed against cardiolipin antigen alone and not against the complexes of cardiolipin bound to exogenous β2-GP1. This method justified the terminology of β2-GP1 independent aCL for sera containing aCL without anti-β2-GP1 antibodies. Absence of anti-β2-GP1 antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen all sera.

The concentration of exogenous β2-GP1 contained in human serum is not significant at a 1/100 dilution (the dilution employed to screen our sera), in comparison with the 10% of calf sera added to the test as source of exogenous β2-GP1 in the assays used for the detection of β2-GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2-GP1) did not react with purified β2-GP1 in the other ELISA test specifically designed to detect anti-β2-GP1 autoantibodies, and therefore which could detect hypothetically high tilters of anti-β2-GP1 antibodies contained in these sera.

Harris's standards were used after calibration of our positive control sera from patients with proven antiphospholipid syndrome (APS), which were considered as positive controls in every microtitration plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera. The antiphospholipid antibodies, including aCL, are directed against several anti-geni targets. Among them, some epitopes are located on the cardiolipin alone. These data were described by Harris when aCL were first characterised in systemic lupus erythematous serum reacting in a VDRL test. By radioimmunoassay, he showed that antibodies contained in these sera were directed against cardiolipin contained in liposomes used as a reagent of the VDRL test. These reagents were constituted by lipids alone without any other cofactor such as β2-GP1. So, Harris's standard can also be used to detect aCL directly only against phospholipid and not against the complex β2-GP1-cardiolipin. In addition, the use of Harris's standards seems to be better adapted to the detection of polyclonal anti-phospholipid antibodies, than monoclonal human aCL used as internal controls. The β2-GP1 used in our assay was provided by Stago laboratories (Asnières, France) and was purified from human sera. We used sodium dodecyl sulphate-polyacrylamide gel electrophoresis and western blotting to ensure that this purified protein was not contaminated.

For every antibody determination, aCL and anti-β2-GP1 autoantibodies, normal levels were established from studies of a large number of normal subjects (blood donors) as previously described.3 4 In this study, 50 serum samples, provided by consenting healthy donors, were tested as controls. Cut-off values were defined as the mean and two standard deviations of the arbitrary units obtained by reference to positive and negative internal standards. For every serum, we defined the corrected optical density (OD) (that is, the mean OD obtained in three coated wells minus the OD corresponding to non-specific binding of each serum, obtained in three uncoated wells). The cut off values defined for anti-β2-GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standard deviation of the anti-β2-GP1 test was applied to positive controls from patients with APS and were used according to previous studies.4 5

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2-GP1 antibodies in normal serum samples. Only 3% of normal sera samples were <3%. These differences between our results and those of Ambrozic et al are probably associated with a differing sensitivity and specificity of the methods between the two laboratories.

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References

Methotrexate and postoperative complications
Grennan et al report the safety of continued methotrexate in the perioperative period.6 Previous investigators have despaired of answering this question definitively owing to the difficulty in recruiting subjects. It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of early complications.2

Despite this important finding, we believe that the results of this study should be regarded with some reservation: continuation of methotrexate throughout the perioperative period should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate-related pancyclopenaemia.8 9 Indeed, in a community-based, observational study of methotrexate use in 460 patients we found the
perioperative period to be especially hazardous for patients with renal impairment and sepsis. Two subjects developed pancytopenia under these conditions, one of whom died.

Although all consecutive patients were included in the study by Grennan et al., it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made about the prevalence of this in the study group. It is important to note that this is a study of methotrexate use in elective surgery. We suggest caution should be taken in patients with renal impairment (best assessed by creatinine clearance) and in the elderly with comorbid cardiovascular disease when approaching surgery. Sudden volume loss, bleeding, or dehydration will impair methotrexate excretion and increase the risk of bone marrow toxicity in this group. It may be prudent in those assessed as at high risk of this complication to stop methotrexate one week before the operation and restart treatment one or two weeks after the operation, depending on postoperative progress. This time period without methotrexate treatment will not alter disease control in the vast majority of patients, although after four weeks without treatment, most will have a flare of the disease.

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Letters

Proximal myopathy and bone pain as the presenting features of coeliac disease

It is rare for coeliac disease to present only with symptoms of osteomalacia, without the classic symptoms of diarrhoea, steatorrhoea, and abdominal discomfort. A 22 year old woman presented with 18 months of a waddling gait disturbance. Hip and back x rays were normal. She experienced bone pain when being hugged, when laughing, or coughing, and had difficulty standing up from a low chair and holding her arms up to blow-dry her hair. She had extreme tiredness and thought she might have lost some weight, but there were no gastrointestinal symptoms.

On examination, she was pale and had difficulty squatting and holding her arms above her head.

Investigations showed a mild anaemia secondary to B thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphatase of 1375 U/L (normal 30–120 U/L), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.00 mmol/l (0.81–1.4 mmol/l), 25-hydroxy vitamin D <5 nmol/l (15–110 nmol/l), and raised parathyroid hormone 53.1 pmol/l (1.0–6.5 pmol/l).

Investigations were carried out for a malabsorption syndrome. Antigliadin, antiantiendomysial antibodies were strongly positive, and a small bowel biopsy showed almost total villus atrophy, confirming the diagnosis of coeliac disease.

A bone scan demonstrated increased activity throughout the skeleton, consistent with secondary hyperparathyroidism. Osteoporosis was demonstrated by dual emission x ray absorptionometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm² (2.65 SD below the young adult female mean) and the neck of the femur 0.633 g/cm² (2.9 SD below the mean).

Treatment involved a gluten-free diet, ergocalciferol 3000 IU daily, calcium carbonate 600 mg twice a day, slow release ferrous sulphate 350 mg daily, and folate acid 5 mg daily.

Within two months her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphatase reduced to 374 U/L. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm² (mean level for young adult women), and the neck of the femur by 39% to 0.878 g/cm² (0.8 SD below the mean).

She had also gained more than 7 kg in weight, and repeat gastroscopy and duodenal biopsy were normal.

Osteomalacia is now an uncommon disease, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965,1 there have been several case reports of coeliac disease presenting with bone pain, proximal myopathy, radiographic findings of pseudofractures and Looser’s zones, or secondary hyperparathyroidism evident on bone scan.2–4 Most patients were middle aged females responding within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates.5 A recent case finding study of coeliac disease showed that many patients in fact present with non-gastrointestinal symptoms, of which anaemia is the most common.6

Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area secondary to villous atrophy, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.7

Secondary hyperparathyroidism can develop if it did in this case, causing increased bone turnover.8 Low bone mineral density is probably due to a combination of hypocalcaemia, impaired bone mineralisation, and reduced exercise because of skeletal pain and proximal weakness.9

Early diagnosis of coeliac disease is important because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determination of antigliadin and antiantiendomysial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.8 There is a genetic influence on the susceptibility to coeliac disease, with a 10% prevalence rate among first degree relatives. On screening our patient’s relatives, one of two siblings was also found to have coeliac disease. A strong association has been found with HLA-DR3 and DR5/DR7.

Treatment with a gluten-free diet with subsequent villous restitution on repeat biopsy has been associated with rapid gains and even normalisation of bone biomarkers, and the greater the degree of osteopenia, the more rapid the gain.10 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.11 Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.12

Osteomalacia presenting with muscle weakness and aches may be the only presenting features of coeliac disease. Prompt treatment and diagnosis is important because treatment with a gluten-free diet and replacement therapy including vitamin D may lead to rapid and effective recovery.4

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References


Authors’ reply

Dr Wluka draws attention to the potential hazard of methotrexate prescribing in sub-

jects with chronic renal failure and sepsis, and we would not disagree with this point. The risk of surgery is increased by any coincidental medical disease including renal failure and sepsis as well as chronic vascular disease. We noted this in our study.

The role of the doctor/rheumatologist is to ensure that any such chronic medical problems are under optimal control before elective orthopaedic surgery. Methotrexate treatment should not be withdrawn from patients with rheumatoid arthritis if the disease is well controlled before elective surgery. The comments of Dr Wluka do not invalidate this conclusion.

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Plasma and peripheral blood mononuclear cells levels of Zn and Cu among Indian patients with RA

Plasma and serum levels of zinc (Zn) and copper (Cu) have been reported to be altered in patients with rheumatoid arthritis (RA). Few studies have measured these levels in tissues, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of immunological aberrations. In a previous study we measured levels of Zn and Cu in plasma and PBMCs to see if they correlated with disease activity and reported reduced levels of Zn in the serum of patients with active RA.

Patients attending the rheumatology clinic at our institute and satisfying the American College of Rheumatology (formerly American Rheumatism Association) criteria for the diagnosis of RA were studied. Patients were categorised as either active or inactive RA. All patients classified as active RA had at least three of the following: morning stiffness for more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. Both plasma and lysed PBMC samples were read on atomic absorption spectrophotometer (Perkin Elmer, Norwalk, CT) at a wavelength of 213.8 nm for Zn and 324.7 nm for Cu. The atomic absorption spectrophotometer was calibrated with reference standards obtained from Sigma Chemicals Company (St Louis, MA).

Thirty-nine patients (31 women) with RA had a mean (SD) age of 36.2 (8.3) years (range 18–62) and mean disease duration of 55.8 (36.6) months (range 6–168). Twenty patients had inactive and 19 patients active disease, respectively. Twenty-two healthy controls (14 women), well matched for age (mean age 34.2 (6.2) years, range 20–56) with the two patient groups, were studied at the same time. Both patients and controls were of middle socioeconomic status. Table 1 shows the plasma and PBMC levels of Zn and Cu.

Our results are in agreement with earlier studies which showed that plasma Zn levels are significantly lower and plasma Cu levels significantly higher in patients with active RA. Additionally, it is shown here that PBMC levels of these elements have an inverse relation with plasma levels.

With acute inflammation, the acute phase response may move Zn into the liver and the reduced plasma concentration may not be indicative of overall deficiency. Possibly, also, PBMCs may be an additional site to which Zn is moved during inflammatory states. The finding of raised Cu levels in the plasma of patients with active RA is to be expected because of a concomitant rise of ceruloplasmin, which is an acute phase reactant. The reduced levels in PBMCs may signify a movement of Cu from PBMCs to the liver where it is absorbed and attached to ceruloplasmin. Thus the findings of plasma and PBMC Cu levels may merely be a reflection of an acute phase response, and the alterations may be due to increased hepatic synthesis of ceruloplasmin.

The effect of concomitant drugs also needs to be considered. The number of patients receiving non-steroidal anti-inflammatory and second line drugs was similar. None of the patients received corticosteroids in the preceding eight weeks.

It would be premature to speculate about a possible role for supplementation with Zn and Cu for patients with RA. From the results shown in this study, patients with inactive RA had similar levels of Zn and Cu as controls. If the diet of patients with active RA were deficient in Zn (as shown by plasma levels) it would be unlikely to contain an excess of Cu and vice versa for PBMC levels. The more plausible explanation would be that this represents a redistribution of trace elements between plasma and PBMCs, and a control of inflammation would lead to levels close to those seen in controls. Hence, further studies need to be carried out on paired samples in a cohort of patients, once when the disease is active and again when it becomes inactive. If plasma Zn levels decrease with the control of inflammation and attain the levels of controls then there would be no indication for dietary supplementation with these metals.

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References

Essential cryoglobulinaemia (type 1) in three patients characterised by Raynaud’s phenomenon, arthralgia-arthritis, and skin lesions

The relevance of monoclonal gammapathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gammapathy or
paraproteins can be detected in healthy adults and in different disease entities like amyloidosis, malignant proliferative disorders, associated with hepatitis C infections, and rheumatic diseases. The overall incidence of paraproteins in adults is about 1%. This incidence increases in people over 70 and increases with age. When a paraprotein is detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance.

Owing to their immunological properties, paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the so-called cryoglobulins. When cryoglobulins are detected in the serum of a patient, this finding is usually associated with the coexistence of paraproteins. Recently, three patients with a clinical picture of a necrotising vasculitis associated with an essential cryoglobulinaemia (type 1) were admitted to our department. The causative relationship between the cryoglobulinaemia and the clinical symptoms was ruled out by the reduced severity of the clinical signs when paraprotein levels were decreased.

Case reports

Patient A was a 69 year old man who, in May 1999, developed extremely painful purpura of the upper part of the third finger of his left hand. In the following days the upper part of his hand became oedematous and necrotic. Angiography of his arteries showed normal vessels. Immune electrophoresis showed the presence of 8 g/l of an M component (IgG). An assay for the detection of cryoglobulinaemia was positive. Skin biopsies showed a superficial perivascular infiltrate, and no evidence for a granulomatous process was found. The patient was treated with chlorambucil 8 mg daily, which had to be stopped after two weeks when the patient showed signs of haemolysis and, after 8 weeks, experienced severe side effects. The paraprotein was treated with chlorambucil 8 mg daily, which, after two weeks was switched to melphalan (6 mg/m²) and prednisone (60 mg/m²) every four weeks for six months. The M component fell to 2 g/l and the severe Raynaud’s phenomenon disappeared.

Patient C was a 78 year old woman who was admitted to our hospital in May 2000 with cyanosis in both feet, indicating possible arterial occlusion. Both feet were cold and very painful. Angiography showed normal vessels, which strongly suggested vasculitis of the terminal arterial vessels of her feet.

Laboratory examination showed a paraprotein (8 g/l) combined with a cryoglobulinaemia consisting of the monoclonal protein (IgGκ). Other laboratory examinations showed no abnormalities. Virus serology showed a positive cryoglobulin titre. She was treated with chlorambucil (8 mg/day) and prednisone (60 mg/day), which improved the necrosis of her legs. The necrosis of her right leg disappeared and on the left foot the necrosis began to demarcate to the upper part of her foot. While waiting for the complete demarcation so that an amputation could be planned, she developed a sepsis and died.

Few patients with essential cryoglobulinaemia type 1 have been reported. Until now a defined clinical syndrome could never be associated with classification of the cryoglobulins. Overall Raynaud’s phenomenon and necrosis of the skin has been described as in our three patients. None of our three patients showed abnormalities on angiographic examination, which may indicate that only the small vessels are affected in the disease process.

In our patients we were able to show that the cryoglobulins were formed by the monoclonal immunoglobulin. When the serum concentration of the paraprotein was reduced, the disease symptoms in our patients improved. These cases suggest that a paraprotein found in patients with a rheumatic syndrome is not only indicative of a developing malignancy or other disease but may also be interpreted as a causative agent. We conclude that paraproteins seen in rheumatic syndromes have a role in the pathogenesis and should always be treated when serious sympoms are present.

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References


Cryoglobulinaemic vasculitis as presenting manifestation of infective endocarditis

Seromunological alterations, including antibodies and/or cryoglobulins, are common in infective endocarditis (IE), however specific autoimmune disorders, such as cryoglobulinaemic vasculitis (CV) associated with IE have seldom been described. CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and complement components in 70–90% of patients with CV a triggering role of hepatitis C virus (HCV) has been suggested. We report the case of two patients who showed a typical CV with severe neurological involvement as the presenting manifestation of underlying IE.

Case 1

In November 1994 a 63 year old woman presented with fever, purpura, paraesthesia, and pseuodoaxitic gait. Her past clinical history was unremarkable except for a prosthetic implant of the left hip four years previously. Table 1 shows the main clinicoserologi- cal features. Repeated blood cultures were negative. Neurorological examination showed normal tactile sensation in her limbs; mild ideomotor slowing down; shaby movements; and unsteady gait. An electro- physiological study recorded a moderate sensory peripheral neuropathy, while ECG showed atrial fibrillation and, at times, complete atrioventricular block. Brain magnetic resonance imaging showed multiple, T2 weighted high signal intensity, punctiform lesions at the white matter consistent with brain vasculitis. Thus a central and peripheral neuropathy complicating CV was established, and prednisone (50 mg) combined with cyclophosphamide (100 mg) was given daily. However, the patient’s clinical status progressively worsened and, finally, she died owing to cardiorespiratory failure fourteen months from the onset of treatment. Necropsy disclosed severe coarctoid vegetations on the left sided valves infected by *Kangella.*

Case 2

In January 1999 a 77 year old woman with no risk factors for infections presented with fever, purpura, and acroraesthesia. Table 1 shows the main clinical and laboratory features suggestive of CV. Prednisone (25 mg/day) was started, with a rapid clinical improvement. One month later, she had an exacerbation of purpura, paraesthesia, acroraesthesia, and impairment of distal muscle strength. An electrophysiological study confirmed a sensorimotor peripheral neuropathy. Thus a higher steroid dose (50 mg/day) was given. A week later fever persisted and the patient complained of precordial pain and cardiac murmurs were found. A chest x ray examination, abdominal echogra- phy, and echocardiography were normal. Cutaneous purpura biopsy disclosed a leuco- cytoclastic vasculitis. Truncoencephalic magnetic resonance imaging showed multiple, T2 weighted high signal intensity, punctiform lesions at the white matter consistent with brain vasculitis. Thus a central and peripheral neuropathy complicating CV was established, and prednisone (50 mg) combined with cyclophosphamide (100 mg) was given daily. However, the patient’s clinical status progressively worsened and, finally, she died owing to cardiorespiratory failure fourteen months from the onset of treatment. Necropsy disclosed severe coarctoid vegetations on the left sided valves infected by *Kanella.**

Discussion

Our two patients show some interesting peculiarities: the unusual presentation of IE
as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the clinically prevalent CV symptoms together with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the fatal outcome. Previous reports (Medline) show that the association of IE with “asymptomatic” cryoglobulinemia is not uncommon, but only a few studies report IE clinically presenting as CV. This latter presentation can mean a misdiagnosis; moreover, steroid treatment can contribute to masking and worsening of the underlying infectious disorder.

In our patients we can reasonably exclude the possibility that IE represented a complication of the CV. In over 300 of our patients with CV, bacterial manifestations have rarely been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in our two patients had quite unusual clinical and virological characteristics: absence of HCV or other hepatotropic viruses; the presence of particularly severe skin purpura; and the presence of neurological affection as important organ involvement. The peripheral neuropathy, in one case associated with central nervous system vasculitis, was the only prevalent organ manifestation seen in our patients. This is one of the most common clinical manifestations in patients with CV, but the aetiopathogenesis of which is still unclear. In a considerable number of patients with CV, negative blood cultures have also been recorded, often when Gram negative bacteria are involved.

In patient 1, the lack of timely recognition of Kingella by repeated blood cultures was probably due to different reasons, including slow-growing of the agent, low microbial charge in the blood samples, and/or inappropriate use of growth media. However, the negative cultures together with clinical symptoms suggestive for CV, in the absence of relevant features at transthoracic echocardiography at the onset, were sufficient reasonably to exclude a suspicion of IE presenting as CV. In conclusion, CV may represent the presenting manifestation of IE, a life threatening condition for which a timely correct diagnosis and adequate treatment are essential. In patients with CV unreated to HCV infection and with fever unresponsive to steroids it is strongly recommended that other less common, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinic microbiological evaluation, including transfusio- neral neuropathy, in one case associated with carbimazole and thiamazole, have been linked. Furthermore, ANCA positivity has been described in the course of Graves’ disease without vasculitis.

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease.

We retrospectively examined 35 serum samples from patients with Graves’ disease. Diagnosis of the disease was based on typical signs and symptoms of hyperthyroidism, raised serum triiodothyronine and thyroxine, very low or undetectable thyroid stimulating hormone, and increased thyroid radioactive iodine uptake. All patients had been receiving treatment with carbimazole (30–45 mg) for at least two months. None of the patients were treated with propylthiouracil or any drug affecting the immune function. ANCA antibodies were determined by indirect immuno- fluorescence (IF) on ethanol fixed granulocytes, as described elsewhere.

Staining patterns were described as cANCA, when a diffuse granular cytoplasmic staining with central accentuation was seen, as pANCA, when perinuclear pattern was observed, and as XANCA when a distinct, homogeneous, non-granular cytoplasmic staining pattern was seen. Autoantibodies against protein 3 and myeloferodase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere.

H. Hospital Universitari Germans Trias i Pujol is a 553 bed hospital situated on the outskirts of Barce- lona. It is a referral hospital serving a population of 700 000 inhabitants. The immunology laboratory is a reference centre.

ANCA (IF) were detected in 21 (60%) of the serum samples. The titre ranged from 1/40 to 1/2560. The immunofluorescence staining pattern was as follows: nine (26%) pANCA, seven (20%) XANCA, and five (14%) cANCA. ELISA was positive in just one case (for MPO)—in the patient with an IF titre of 1/2560. Our results are very similar to those of Aeltra et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with Graves’ disease.

The IIF staining pattern was cANCA in five cases and XANCA in one case. Anti-MPO anti- bodies were detected only in one (5%) of the patients. In our study ANCA were detected in 21 (60%) serum samples. The IIF staining patterns were more heterogeneous, but the ELISA results were similar.##

### References


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**Table 1** Epidemiological, clinical, and seroomunological features in two female patients with infective (bacterial) endocarditis, at the first visit

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
</tr>
<tr>
<td>Disease duration (weeks)</td>
<td>7</td>
</tr>
<tr>
<td>Purpura</td>
<td>Haemorrhagic papulonodular</td>
</tr>
<tr>
<td>Weakness</td>
<td>Severe</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Hepatopathy</td>
<td>Absent</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Absent</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>Peripheral + central</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>Absent</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>83</td>
</tr>
<tr>
<td>CRP (normal ≤ 5 mg/l)</td>
<td>53</td>
</tr>
<tr>
<td>WBC (normal 3–10 × 10^9/l)</td>
<td>89 000</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>87</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>10</td>
</tr>
<tr>
<td>γ-Globulinaemia (g/l)</td>
<td>19.5</td>
</tr>
<tr>
<td>RF (normal &lt;20 IU/ml)</td>
<td>575</td>
</tr>
<tr>
<td>C3 (normal 500–1200 mg/l)</td>
<td>930</td>
</tr>
<tr>
<td>C4 (normal 200–550 mg/l)</td>
<td>≤60</td>
</tr>
<tr>
<td>Cryocrit, % (cryo-type)</td>
<td>0.5 (IgG-IgM)</td>
</tr>
<tr>
<td>Hepatitis virus markers*</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*HBSAg, anti-HBs, anti-HBeIgM, anti-HBc; anti-HCV by ELISA and RIBA; anti-EBV IgM, anti-HIV.
Lupus relapse after prostaglandin E₁, administration: activation of a cytokine cascade?

A variety of abnormalities in cytokine production occur in human and murine lupus, but their specific role in lupus pathogenesis is unknown. Recent in vitro studies emphasise the role of prostaglandins in the cytokine induction and modulation of the humoral immune response. We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E₁ (PGE₁) administration, which to our knowledge has not been previously reported. A 25-year-old woman was admitted to hospital to receive treatment with IV PGE₁, owing to severe Raynaud’s phenomenon. Fifteen years previously SLE had been diagnosed according to the American Rheumatism Association criteria, with renal biopsy proven diffuse proliferative lupus glomerulonephritis (WHO class IV). A previous examination showed only painful, violaceous, and atrophic finger pads with no signs of systemic inflammatory disease. The chest X-ray films were normal and laboratory investigations showed antinuclear antibodies (ANA; titre 1:160) and hypocomplementaemia (C₃ 0.6 g/l, C₄ 0.1 g/l), with normal liver, renal, and haematological parameters. Treatment with 40 mg/12 h IV PGE₁ was started. On the sixth day of treatment the patient began to have chest pain, fever, dyspnoea, and pericardial friction rub. The laboratory showed anaemia, modest thrombocytopenia, and ANA 1:320, with no changes in the rest of the biochemical serum parameters. Echocardiography and chest X-ray examination showed moderate pericardial and bilateral pleural effusions. PGE₁ was withdrawn and oral prednisone, 60 mg/day, was started with prompt improvement in the symptoms.

We investigated the possibility that PGE₁ mediated cytokine production might be the cause of the relapse of SLE in this patient. Intracellular expression of cytokines in the patient’s T lymphocytes after specific PGE₁ stimulation was determined by flow cytometry using cytokine conjugates in combination with surface anti-CD3 (Pharmingen, San Diego, CA), as previously described. The test performed eight months after the PGE₁ treatment showed a dramatic rise in interleukin (IL) 4 production (table 1). It has been suggested that cytokines have an important role in the immune dysregulation seen in lupus prone mice and in patients with SLE. Increasing evidence supports a role for T helper cell type 2 (Th2) cytokines, such as IL4, in promoting and perpetuating B cell hyperactivity and autoantibody formation. A change in the proportion of Th2 cytokines might be associated with the polyclonal B cell activation seen in SLE. Restoration of Th1 and Th2 cytokines to levels similar to those seen in healthy mice results in amelioration of the clinical manifestations of an already established experimental SLE.

On the other hand, studies in vitro in this patient, may be a marker of dysregulation of the Th1/Th2 profile and might have been the cause of her lupus relapse.

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References
2 Shreedar V, Giuse T, Sung VW, Ullrich SE. A cytokine cascade including prostaglandin E₂, IL-4, and IL-10 is responsible for UV-induced systemic immune suppression. J Immunol 1998;160:3783–9

Table 1 Intracellular cytokine production after PGE₁ stimulation in the patient and in an asymptomatic lupus patient who served as a control. Results are shown as the percentage of T lymphocytes with cytokine synthesis

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE₁</td>
<td>Basal PGE₁</td>
<td>Basal PGE₁</td>
</tr>
<tr>
<td>Patient</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Control</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

IL, interleukin; INFγ, interferon γ.

Whole blood was incubated with or without PGE₁, 10 ng/ml, for six hours in the presence of Brefeldin A. Cells were stained with FITC-anti-CD3 and, after erythrocyte lysis and permeabilisation, with the phycoerythrin conjugated anti-interleukins. Samples were analysed by flow cytometry.

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Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation. Synovial and serum osteocalcin correlate positively. In ankylosing spondylitis (AS) the serum concentration has been reported to be low or normal. Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.

To answer the question whether serum osteocalcin is a useful marker of disease activity in AS, longitudinal studies may be more sensitive and specific. For this reason changes in serum osteocalcin were correlated with changes in ESR, which is probably still the best marker of inflammation in AS.

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age 43 (11) years; disease duration 14 (4) years; 75 male, 14 female; age 43 (11) years; disease duration 14 (4) years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, electrotherapy, underwater exercises, and raft treatment as prescribed by the patient’s doctor. Patients were advised not to change their drug treatment. The ESR was determined according to the Westergren method, the result at one hour being used for calculation. Serum was frozen at −18°C until further analysis. Osteocalcin was measured in one batch with a commercially available kit (IRMA, Biocis, Vienna; normal range according to the manufacturer 7.5–31.5 ng/ml in men, 3.7–31.7 ng/ml in women). Results are given as median (25th, 75th centile). The Mann-Whitney rank sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 18 (8, 28) mm/1st h, serum osteocalcin 25 (20.5, 52.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/1st h, serum osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR and osteocalcin at the first examination did not correlate significantly (r=0.07; p=0.5). The changes in ESR (1 (−4, 6) mm/1st h) and changes in osteocalcin (−0.5 (−2.6, 5.7) ng/ml) showed a significant correlation (r=−0.28; p<0.01).

The results confirm previous findings showing no significant correlation between serum osteocalcin and ESR in cross sectional studies. Changes in osteocalcin after three weeks, however, correlated significantly with changes in ESR, but in view of the weak correlation (r=−0.28) the clinical relevance of serum osteocalcin determination for assessing disease activity seems limited.

Table 1: Immunological data of the patient

<table>
<thead>
<tr>
<th>Values</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyphocyte count (10 9/l)</td>
<td>1.5</td>
<td>&gt;2</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>23.3</td>
<td>(8.4–19.4)</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>6290</td>
<td>(620–3980)</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>531</td>
<td>(240–3920)</td>
</tr>
<tr>
<td>CD3 (10 9/l)</td>
<td>1.2</td>
<td>0.7–4.2</td>
</tr>
<tr>
<td>CD4 (10 9/l)</td>
<td>2.0</td>
<td>0.3–2.0</td>
</tr>
<tr>
<td>CD8 (10 9/l)</td>
<td>1.0</td>
<td>0.3–1.8</td>
</tr>
<tr>
<td>CD19 (10 9/l)</td>
<td>0.3</td>
<td>0.12–3.6</td>
</tr>
<tr>
<td>CD3/CD16+CD56 (10 9/l)</td>
<td>0.2</td>
<td>0.1–0.9</td>
</tr>
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</table>
Henoch-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-nuclear antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.3

Low CD4+ T lymphocyte counts are rare in the absence of immunodeficiency, most commonly infection with HIV.4 In our patient, major histocompatibility complex class II deficiency was excluded by the expression of HLA-DR on peripheral blood lymphocytes. Serological testing for HIV infection was negative and, additionally, the patient had no risk factor for transmission of HIV infection or recent immunosuppressive treatment.

All patients with idiopathic CD4+ T lymphopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4×10⁹/l, to determine the natural history of their infections and lymphopropenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients.5 Two recent preliminary reports suggest the presence of a retrovirus in affected patients.

Low CD4+ T lymphocyte counts reflect transient responses to infections or other conditions such as autoimmune disorders.4 In patients with aorta arteritis, immunological investigations have shown a decrease in the titre of complement and phagocytic activity of neutrophil granulocytes, deep depression of T cell immunity, and hypergammaglobulinaemia.6 Wiskott-Aldrich and Takayasu arteritis have been reported previously.7 It is rare for patients to have both disorders and with this case report, we draw attention to this association. This case report suggests that low CD4+ lymphopenia may cause dysgammaglobulinemia and autoimmune syndromes such as Takayasu arteritis.

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References

Recurrent orbital pain and diplopia in a 12 year old boy

A previously healthy 12 year old boy was referred to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia. The first disease manifestation had started three years before, when the patient suddenly presented with diplopia and painful periorbital oedema. Limited abduction of the right eye was present. The treating ophthalmologist, after a thorough investigation that excluded brain tumours, orbital masses, and myasthenia gravis, prescribed naproxen (20 mg/kg/day) and systemic corticosteroid treatment (prednisone 1 mg/kg/day, tapered and withdrawn within 15 days); symptoms resolved completely within two weeks. A first magnetic resonance imaging (MRI) scan of the orbit had shown first degree exophthalmus of the right eye and oedema and thickening of the left medial rectus muscle (fig 1). Since then the boy had many episodes of ocular pain and diplopia, lasting from two to four weeks, affecting both eyes or alternatively the right and the left, at intervals of up to three months. No sequelae were detected after each relapse.

During the last relapse in October 1999, naproxen and high dose oral corticosteroid treatment (prednisone 2 mg/kg/day) were required to control the disease activity, which subsided over a period of two months. After a short period of wellbeing, the disease flared up again, and recurrence of orbital pain and diplopia was observed when steroids were reduced to 0.5 mg/kg/day. The boy was then admitted to our unit. He appeared well, with no constitutional symptoms. Ocular examination showed mild right exophthalmus and limited motion of both eyes.

Laboratory tests including muscle enzymes (alanine aminotransferase, aspartate aminotransferase, creatinine kinase, lactate dehydrogenase, aldolase) values, complement levels, and thyroid function were all within the normal range. Serological tests were negative for viral and bacterial infections, and antibodies against Borrelia burgdorferi were absent. Autoantibodies (antinuclear antibodies, anti-dsDNA, anticyclic citrullinated peptide antibodies) were undetectable. Other markers that are considered measures of disease activity in juvenile inflammatory myopathies were evaluated: factor VIII related antigen levels were raised, while neopterin levels and the number of circulating B lymphocytes (CD19 positive cells) were normal. Electrocardiography and two dimensional echocardiography excluded a concurrent myocarditis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (Scl), Crohn’s disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extrinsic and of the right medial rectus muscles. Electromyography showed increased insertional activity, fibrillations, and positive sharp waves. Ocular myositis was diagnosed. The oral prednisone dose was raised to 30 mg/day, and rapidly tapered after improvement of signs and symptoms. In November 2000, cyclosporin (3 mg/kg/day) was introduced; no relapse of the ocular findings has been seen so far, and prednisone has been progressively reduced to the current dose of 5 mg/day.

The group of idiopathic inflammatory myopathies encompasses a variety of common and uncommon syndromes. The uncommon variants of myositis include orbital myositis, a condition that is rare in adults and even rarer in children.10 Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, Scl, giant cell myocarditis, and Crohn’s disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease, ocular myopathies, such as mitochondrial disorders and ocular dystrophies; and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinus thrombosis are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extraocular muscles.
muscles. MRI shows muscle oedema of the affected muscle(s), and is useful for monitoring disease activity. Non-steroidal anti-inflammatory drugs are recommended as first line treatment, but systemic steroids are required in most cases. When steroids fail to control muscle inflammation, methotrexate and cyclosporin have been used with success. In our patient, cyclosporin was successful as a steroid sparing agent, because a rapid recurrence of symptoms had always occurred in the past when the corticosteroid dose was reduced, and at present, after six months of cyclosporin treatment, the boy is still asymptomatic and receiving a low dose of steroids.

Despite the rarity of this disorder, our case suggests that diplopia in a child requires rapid and extensive investigation to must include isolated ocular myositis in the differential diagnosis.

**References**

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**Sciatia or spinal lymphoma**

The involvement of the central nervous system and vertebrae by low grade non-Hodgkin's lymphoma is rare. In a previous "lesson of the month" in this journal, it was implied that there is always a bad prognosis for patients with spinal lymphoma; however, milder cases may also occur.

A 71 year old man presented to us in January 2000 with a three month history of severe low back pain affecting mainly the left lumbar area and buttock, radiating to the outer aspect of the left thigh and calf. He did not have bladder symptoms or history of recent falls. On examination, he looked well; there was no lymphadenopathy. He had restricted back movement with tenderness of lower lumbar spinal processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and coordination. Knee jerks were reduced, ankle jerks were absent, both plantars were down going, and there was no sensory deficit.

He had a past history of epilepsy, which was controlled by phenytoin and phenobarbitone. In 1995 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypersplenism. Spleenectomy was performed in 1994, his blood count returned to normal, and repeated full blood counts were stable. In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis and degenerative changes.

Investigations showed normal serum biochemistry apart from a mild increase of alkaline phosphatase, which was 242 IU/l (normal 60–220). The total white cell count was 24.7×10⁹/l, differential count showed neutrophils 3.5×10⁹/l (14%), lymphocytes 17×10⁹/l (69%), monocytes 4.0×10⁹/l (16.0%), eosinophils 0.2×10⁹/l (1.0%), basophils 0.0×10⁹/l (0.0%), and occasional atypical lymphocytes were seen in blood film. The erythrocyte sedimentation rate was 4 mm/1st h, a myeloma screen was negative, and prostate specific antigen was normal.

A lumbosacral spine x ray examination showed biconcave L3 with diffuse osteopenia. Abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotope scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes.

An MRI scan showed extensive infiltration involving vertebral bodies and appendages throughout the lumbosacral spine, being most intense at the biconcave L3; the appearance was consistent with lymphoma or myeloma (fig 1).

During his stay in hospital, the patient's pain resolved completely after treatment with non-steroidal anti-inflammatory drugs, analgesics, and physiotherapy. His haematologist started treatment of the patient with chlorambucil 10 mg/day for 10 days to be repeated every three weeks, these cycles to be continued for 12 months.

Eight months after the diagnosis of spinal lymphoma, the patient has remained well and active; his back pain is minimal.

In rheumatology, it is essential to differentiate between malignant disease and the more common causes of back pain. Our patient was in a good physical condition, which is unusual for someone with malignancy, his presentation with low back pain appeared to be a typical case of sciatia, and the pain settled down with conventional treatment. Clinically there was no evidence of recurrence of lymphoma—for example, enlarged lymph nodes, weight loss, or fever. However, because of his age at presentation and significant past history thorough investigations were mandatory.

**Unusual complications in the Churg-Strauss syndrome**

Although abdominal complications are occasionally reported in the Churg-Strauss syndrome (CSS), bowel perforations, cholecystitis, eosinophilic peritonitis, and oophoritis are very unusual and normally resolve after immunosuppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

A 64 year old woman with a 13 year history of urticaria, recurrent rhinitis, and asthma was admitted for abdominal pain. An increasing peripheral eosinophilia rising from 1% to 22% in the past five years was detected. Two years before hospital admission an extensive urticarial erythema developed. An abdominal ultrasonography performed during an asthmatic exacerbation when she had no abdominal pain disclosed a thick-walled gall bladder with no echogenic contents. An excised nasal polyp showed polymoid hyperplasia with many eosinophils.
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 1×10^9/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed acalculous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right anexectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.89×10^9/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/h, rheumatoid factor (RF) 765 IU/ml (normal <80), and total IgG 769 IU/ml (normal <80), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antineutrophil cytoplasmic antibody values were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaline and hyaline casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 25 g/l, a leucocyte count of 1.05×10^9/l with 80% eosinophils, and fever, ileus, and vomiting, and she died 48 hours later. A necropsy was not allowed.

Abdominal pain is reported in up to 25–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described, the last of these being responsible for up to 10% of the CSS deaths. Acalculous cholecystitis, although very rare, may be the first and sometimes the unique manifestation of the CSS. Its evolution is usually torpid, and sometimes only diagnosed at necropsy. Abdominal ultrasonography should be included in the routine screening of patients with CSS.

The right oophoritis was due to vasculitis, with an eosinophilic infiltrate suggestive of CSS (fig 1). As far as we know, this is the first reported case of CSS with confirmed ovarian involvement.

The ascitic fluid, rich in eosinophils, the eosinophilic infiltration of major omentum samples and the clinical evolution suggest that the peritoneal involvement was due to the CSS, an extremely rare complication of this disease. Eosinophilic peritonitis was suggested by Lanham owing to serosal involvement. Eosinophilic peritonitis was suggested by Lanham owing to serosal involvement. The right oophoritis was due to vasculitis, with an eosinophilic infiltrate suggestive of CSS (fig 1). As far as we know, this is the first reported case of CSS with confirmed ovarian involvement.

In summary, CSS abdominal complications should be promptly suspected and treated. In addition, CSS ovarian involvement, although rare, should be included in the differential diagnosis of ovarian vasculitis.

Figure 1 Ovarian eosinophilic infiltration is located in the hilum area, where eosinophilic arthritis is found (haematoxylin and eosin ×25, and left lower quadrant ×200).

References
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Fax: +31 (0)71 526 6752  
Email: F.C.Breedveld@lumc.nl  
Website: www.eurr.org

Tenth Intensive Applied Epidemiology Course for Rheumatologists  
11–15 Mar 2002; Manchester, UK  
No previous experience in epidemiology is needed. The course is residential and limited to 29 places  
Contact: Ms Lisa McClain, ARC Epidemiology Unit, University of Manchester, Oxford Road, Manchester M13 9PT, UK  
Tel: +44 (0)161 275 5993  
Fax: +44 (0)161 275 5043  
Email: Lisa@fsl.ser.man.ac.uk

International Congress: New Trends in Osteoarthritis  
9–11 May 2002; Milan, Italy  
Contact: Organising Secretariat, O.l.c. S.r.l., Via Fatebenefratelli 19, 20121 Milan, Italy  
Tel: +39 02 65 71 200  
Fax: +39 02 65 71 270  
Email: osteoarthritis@oic.it

10F World Congress on Osteoporosis  
10–14 May 2002; Lisbon, Portugal  
Contact: Iof Secretariat, 71 cours Albert Thomas, F-69003 Lyon, France  
Tel: +33 472 91 41 77  
Fax: +33 472 36 90 52  
Email: info@ioflyon.org  
Website: www.osteofound.org

5th European Conference on Systemic Lupus Erythematosus  
26–30 May 2002; Athens, Greece  
Chairman Professor HM Moutsopoulos  
Secretariat: Amplification Congress Organising Bureau  
Email: h.moutsopoulos@med.uoa.gr  
Website: www.amplification.gr

Annual European Congress of Rheumatology  
12–15 June 2002; Stockholm, Sweden  
Contact: Fred Wyss, Executive Secretary EULAR, Wiltenkirscherstrasse 15, CH-8032, Zurich, Switzerland  
Tel: +41 1 383 9690  
Fax: +41 1 383 9810  
Email: eular@bluewin.ch  
Website: www.eular.org

10th International Congress on Behçet’s Disease  
27–29 June 2002; Berlin, Germany  
Under the auspices of the International Society for Behçet’s Disease  
Up to eight young investigator awards, each of $500, will be awarded on the basis of abstracts submitted  
Contact: Professor Ch Ch Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabenckstrasse 60–62, 14195 Berlin, Germany  
Fax: 49 30 84456908  
Email: zoubbere@zedat.fu-berlin.de  
Website: www.userpages.fu-berlin.de/~zoubbere  
ISBD website: www.behcet.ws

29th Scandinavian Congress of Rheumatology  
15–18 Aug 2002; Tromso, Norway  
Contact: Hans Nossent, Department of Rheumatology, University Hospital Tromso, Norway  
Tel: 47 776 27294  
Fax: 47 776 27258  
Email: 29scr2002@rito.no or revhan@rito.no

Translational Research in Autoimmunity  
21–22 Sep 2002; Pavia, Italy  
Contact: Organising secretariat: eventi S.R.L., Corso Cavour, 1820 – 27100 Pavia, Italy  
Email: tra@e20pr.com  
Website: www.e20pr.com  
Congress website: www.medicine.ucsd.edu/albani/2001meeting

OsteoArthritis Research Society International (OARSI) World Congress  
22–25 Sep 2002; Sydney, Australia  
Contact: OsteoArthritis Research Society International (OARSI), 2025 M Street, NW, Suite 800, Washington DC 20036, USA  
Tel: +1 202 367 1177  
Fax: +1 202 367 2177  
Email: oarsi@oarsi.org  
Website: www.oarsi.org

10th International Congress on Antiphospholipid Antibodies  
29 Sep–3 Oct 2002; Sicily, Italy  
Deadline for abstracts 1 April 2002  
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kenes International, PO Box 50006, Tel Aviv 61500, Israel  
Tel: 972 3 5140018 9  
Fax: 972 3 5172484  
Email: aps@kenes.com  
Website: www.kenes.com/aps

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases  
14–17 Oct 2002; Nashville, Tennessee, USA  
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA  
Tel: (615) 343 7329  
Fax: (615) 343 7534  
Website: www.eicosanoids.science,eayne.edu

66th American College of Rheumatology AGM  
25–29 Oct 2002; New Orleans, USA  
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 250, Atlanta, Georgia 30045–4300, USA  
Tel: +1 404 633 3777  
Fax: +1 404 633 1870  
Email: acr@rheumatology.org  
Website: www.rheumatology.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis  
7–9 November 2002; Barcelona, Spain  
Contact: Yolande Piette Communication, Boulevard Kleyer 108, 4000 Liège, Belgium  
Tel: 32 4 254 12 25  
Fax: 32 4 254 12 90  
Email: ypc@compuserve.com

Certifying Examination in Pediatric Rheumatology  
18 Nov 2002  
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA  
Tel: 919 929 0461  
Fax: 919 918 7114 or 919 929 9255  
Website: www.abp.org

Future EULAR congresses  
18–21 June 2003; EULAR 2003 Lisbon, Portugal  
9–12 June 2004; EULAR 2004 Berlin, Germany  
8–11 June 2005; EULAR 2005 Vienna, Austria  
21–24 June 2006; EULAR 2006 Amsterdam, The Netherlands