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 antibody” was somewhat misleading. The term was introduced and abbreviated as “aCL,” a group of antibodies detected in many conditions, but the β2 glycoprotein 1 (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.3 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,4 the units should be abbreviated as GPl. (for IgG) and MPL (for IgM) as previously defined.5 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 predominantly, 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 recognised β2GPI associated with cardiolipin. We reported this binding pattern for anti-β2GPI in children with atopic dermatitis,6 and the same was shown also for some patients with autoimmune diseases, including APS.7

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.8 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, 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 assays were calibrated with β2GPI dependent monoconal aCL (IgG and IgM anti-β2GPI ELISA and β2GPI dependent aCL ELISA) and positive in-house standards (all IgA assays and β2GPI independent aCL ELISA). The cut-off values for anti-β2GPI were set as described9 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.10 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 ensured right 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=53)</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>12</td>
<td>22</td>
</tr>
<tr>
<td>RA - RF (n=17)</td>
<td>1</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

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

If you have a burning desire to respond to a Letter To The Editor published in the Annals of the Rheumatic Diseases, why not make use of our “rapid response” option?

Log on to our website (www.annrheumdis.com), find the paper that interests you, and send your response via email by clicking on the “eLetters” option in the box at the top right hand corner.

Providing it isn’t libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on “read eletters” on our homepage.

The editors will decide as to whether also to publish it in a future paper issue.

www.annrheumdis.com
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-β2GP1 and β2GP1 dependent aCL of IgA isotype. Interestingly, 3/11 RA sera which showed binding to β2GP1 adsorbed on a high binding plate did not recognize β2GP1 associated with cardiolipin, as already reported.2 In contrast, 3/9 RA sera binding to β2GP1 complexed with cardiolipin did not recognize β2GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2GP1 in RA, which may differ in fine specificity between anti-β2GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β2GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β2GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GP1 (10 µg/ml) lowered the binding of β2GP1 independent aCL by about 50%, most probably owing to the competition between β2GP1 independent aCL and β2GP1 for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2GP1 and β2GP1 dependent aCL, which might be associated with the signs of APS. The importance of distinguishing β2GP1 independent aCL has not been fully clarified. It seems possible that β2GP1 independent aCL do not confer an increased risk for APS in RA.

A Ambrozic, B Bozic, M Hoinjak, T Kveder, B Rozman
Department of Rheumatology, University Medical Centre Ljubljana, Slovenia

Correspondence to: Dr A Ambrozic, Department of Rheumatology, University Medical Centre, Vodnikova 62, 1000 Ljubljana, Slovenia [SIL; ales.ambrozic@umlj.si]

References

Authors’ reply
In response to the comments of Ambrozic et al we would like to make a few comments to the data published earlier in the Annals.3,4 The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera by the dependence of aCL on β2-glycoprotein 1 (β2GP1). It is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2GP1 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 alone and not against the complexes of cardiolipin bound to exogenous β2GP1. This method justified the terminology of β2GP1 independent aCL for sera containing aCL without anti-β2GP1 antibodies. The absence of anti-β2GP1 antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen all sera.

The presence of anti-β2GP1 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 β2GP1 in the assays used for the detection of β2GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2GP1) did not react with purified β2GP1 in the other ELISA test specifically designed to detect anti-β2GP1 autoantibodies, and therefore which could detect hypothetically high titres of anti-β2GP1 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 we considered as the 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.3 The antiphospholipid antibodies, including aCL, are directed against several anti-gpogenic targets. Among them, some epitopes are located on the cardiolipin alone. These data were described by Harris when aCL were first characterized in systemic lupus erythematosus 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.3,4 These reagents were constituted by lipids alone without any other cofactor such as β2GP1. So, Harris’s standard can also be used to detect aCL directed only against phospholipid and not against the complex β2GP1-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 β2GP1 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-β2GP1 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 determined 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-β2GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2GP1 test were prepared to controls from patients with APS and were used according to previous studies.3,4 In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2GP1 antibodies in normal sera. The percentage of positive normal serum samples was <3%. These differences between our results and those of Ambrozic et al are probably associated with a differing sensitivity of the assays and the methods of the two laboratories.

M O Jauberteau
Department of Immunology, University of Limoges, France

C Bonnet
Department of Rheumatology, University of Limoges, France

Correspondence to: Dr C Bonnet, Department of Rheumatology, Centre Hospitalier de Limoges, 2 Avenue Martin-Luther King, 87042 Limoges cedex, France

References

Methotrexate and postoperative complications
Grennan et al report the safety of continued methotrexate in the perioperative period. 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 complications.

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 was not accompanied by significant cautio.
perioriperal period to be especially hazardous for patients with renal impairment and sepsis. Two subjects developed pancycopenia 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 affect disease control in the vast majority of patients, although after four weeks without treatment, most will have a flare of the disease.

A Wluka
Department of Epidemiology and Preventive Medicine, Monash University, Australia

R Buchbinder
Department of Epidemiology, Cabrini Hospital, Malvern, Australia and Monash University, Australia

S Hall
Cabrini Medical Centre, Malvern, Australia

G Littlejohn
Monash Medical Centre, Clayton, Australia

Correspondence to: Dr A Wluka, Department of Epidemiology and Preventive Medicine, Monash University, Central and Eastern Clinical School, Alfred Hospital, Prahran, Victoria 3181, Australia

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 coinciden-
tial 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 prob-
lems are under optimal control before elective orthopaedic surgery. Methotrexate treatment should not be withdrawn from patients with rheumatoid arthritis if the disease is well con-
trolled before elective surgery. The comments of Dr Wluka do not invalidate this conclusion.

D M Grennan, J Gray
Department of Rheumatology, Wrightington Hospital NHS Trust, Hall Lane, Apley bridge, Wigan WN6 9EW, UK

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 laugh-
ing, 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 gastro-
intestinal symptoms. On examination, she was pale and had dif-
ficulty squatting and holding her arms above her head.

Investigations showed a mild anaemia sec-
ondary to β thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphatase of 1375 U/l (nor-
mal 30–120 U/l), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.13–2.65 mmol/l), phosphate 1.0 mmol/l (0.8–1.4 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 malab-
sorption syndrome. Antigliadin, antientomy-
sial, and antiglutamin antibodies were strongly positive, and a small bowel biopsy showed almost total villus atrophy, confirm-
ing 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 absorptiometry 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, ergo-
calcirol 3000 IU daily, calcium carbonate 600 mg twice a day, slow release ferrous sulphate 350 mg daily, and folic acid 5 mg daily.

Within two months she had bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphatase re-
duced to 374 U/l. Bone mineral density had increased markedly after 12 months of treat-
ment, 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 gastrointestinal and duodenal biopsy were normal.

Osteomalacia is now an uncommon dis-
case, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965, there have been several case reports of coeliac disease presenting with bone pain, proximal myop-
athy, radiographic findings of pseudofractures and Looser’s zones, or secondary hyperpara-
thyroidism evident on bone scan. Most patients were middle aged and responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates. 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.

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 dietary fatty acids to form insoluble calcium soaps.

Secondary hyperparathyroidism can de-
velop as it did in this case, causing increased bone turnover. Low bone mineral density is probably due to a combination of hypocalca-
emia, impaired bone mineralisation, and re-
duced exercise because of skeletal pain and proximal weakness.

Early diagnosis of coeliac disease is impor-
tant because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determina-
tion of antigliadin and antientomyosial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%. 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 sub-
sequent villous restitution on repeat biopsy has been associated with rapid gains and even normalisation of bone biomarkers; the greater the degree of osteopenia, the more rapid the gain. The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix. Introduction of hormone replacement therapy in women approaching the meno-
pause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.

Osteomalacia presenting with muscle weakness and aches may be the only present-
ing features of coeliac disease. Prompt treat-
ment and diagnosis is important because treatment with a gluten free diet may not be suffi-
cient, and vitamin D may lead to rapid and effective recovery.

M Wong, J Scally, K Watson, J Best
University of Melbourne Department of Medicine, St Vincent’s Hospital, Melbourne, Victoria, Australia; m.wong@bigpond.com

References

1 Mass AJ, Waterhouse C, Terry R. Gluten-sensitive enteropathy with osteomalacia

www.annrheumdis.com

Ann Rheum Dis: first published as 10.1136/ard.61.1.86 on 1 January 2002. Downloaded from http://ard.bmj.com/ on June 16, 2022 by guest. Protected by copyright.


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). One of the major hypotheses is that the increased levels of plasma copper in patients with active RA signify a movement of Cu from PBMCs to the liver where it is absorbed and attached to some unknown complex. This may decrease plasma levels of Zn and increase the number of PBMCs containing Zn. The reduced levels in PBMCs may be due to the fact that the PBMCs do not have the ability to transport Zn into the cells. This decrease in Zn levels in PBMCs may also be due to the fact that the PBMCs do not have the ability to transport Zn into the cells.

**Table 1** Copper and zinc levels in plasma and PBMCs of patients with RA. Results are given as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma zinc (µg/dL) 1</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>Plasma Cu (µg/dL) 2</td>
<td>135.2 (28.6)</td>
<td>108.3 (38.4)</td>
<td>121.4 (34.4)</td>
<td>98.4 (16.4)</td>
</tr>
<tr>
<td>Plasma Cu (µg/10^6 cells) 3</td>
<td>164.6 (357)</td>
<td>1016 (296)</td>
<td>1426 (324)</td>
<td>946 (446)</td>
</tr>
<tr>
<td>Plasma Cu (µg/10^6 cells) 4</td>
<td>50.8 (43.2)</td>
<td>86.4 (33.2)</td>
<td>74.3 (38.2)</td>
<td>104.2 (8.5)</td>
</tr>
</tbody>
</table>

PBMCs, peripheral blood mononuclear cells; there was no correlation between age, duration of disease, rheumatoid factor positivity, or any other variable with plasma or PBMC levels of Zn and Cu.

Overall plasma levels were significantly lower among patients than controls (p<0.05) and patients with active RA had lower levels than those with inactive RA (p<0.05). There was no correlation between plasma copper levels and age, duration of disease, rheumatoid factor positivity, or any other variable with plasma or PBMC levels of Zn and Cu.

1 Plasma copper levels may merely be a reflection of plasma Zn levels since plasma Zn levels are significantly higher in patients with active RA.

2 Plasma levels of Zn and Cu were significantly lower among patients than controls (p<0.05). There was no correlation between plasma copper levels and age, duration of disease, rheumatoid factor positivity, or any other variable with plasma or PBMC levels of Zn and Cu.

3 PBMC levels of Zn and Cu were significantly lower among patients than controls (p<0.05) and patients with active RA had lower levels than those with inactive RA (p<0.05). There was no correlation between PBMC copper levels and age, duration of disease, rheumatoid factor positivity, or any other variable with plasma or PBMC levels of Zn and Cu.

4 PBMC levels of Zn and Cu were significantly lower among patients than controls (p<0.05) and patients with active RA had lower levels than those with inactive RA (p<0.05). There was no correlation between PBMC copper levels and age, duration of disease, rheumatoid factor positivity, or any other variable with plasma or PBMC levels of Zn and Cu.

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 in adults is about 1%.\(^2\) The overall incidence of paraproteins in adults is about 1%.\(^2\) This incidence is higher in people over 70 and increases with age.\(^2\) When a paraprotein is detected and no underlying disease is present, the 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.

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 left hand became necrotic. Angiography of his arteries showed normal vessels. Immune electrophoresis showed the presence of 8 g/l of an M component (IgG\(^\lambda\)). An assay for the detection of cryoglobulinaemia was positive. Laboratory tests showed a normal plasma viscosity; anticardiolipin antibodies could not be detected and neither could rheumatoid factor. Complement components showed decreased C4 levels (46 IE/ml (normal 81–128), C3 1.3 g/l (normal 0.9–1.8), and low C4 levels 35 mg/l (normal 150–400)). Virus serology was negative for cytomegalovirus, hepatitis A, B, and C. A skin biopsy of non-affected skin showed only a slight epidermal thickening and histopathological examination of a skin biopsy showed normal vessels. The M component was detected with chlorambucil 8 mg daily and should be treated when serious symptoms are present.

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 paraproteins 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 be treated when serious sympoms are present.

Correspondence to: Dr Swaak

References


Cryoglobulinemia vasculitis as presenting manifestation of infective endocarditis

Seromunomological alterations, including antibodies and/or cryoglobulins, are common in infective endocarditis (IE), however, specific autoimmune disorders, such as cryoglobulinemia vasculitis (CV) associated with IE have seldom been described.\(^3\) CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and complement\(^\ast\) in 70–90% of patients with CV a triggering role of hepatitis C virus (HCV) has been suggested.\(^3\) 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, paraesthesiaes, and pseudoatopic gait. Her past clinical history was unremarkable except for a prosthetic implant of the left hip four years previously. Table 1 shows the main clinico-radiological features. Repeated blood cultures were negative. Neurological examination showed normal sensitivity and coarse loss of sensation in the arms and legs; mild ideomotor slowing down; shaky movements; and unsteady gait. An electroencephalographic study recorded a moderate sensorimotor peripheral neuropathy, while ECG, chest x-ray examination, abdominal echography, and echocardiography were normal. Cutaneous purpura biopsy disclosed a leukocytoclastic vasculitis. Truncocerebral magnetic resonance imaging showed a slight to moderately 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 cardiopulmonary failure a 8 month of treatment. Necropsy disclosed coarse endocardial vegetations on the left sided valves infected by *Kagella*.

Case 2

In January 1999 a 75 year old woman with no risk factors for infections presented with fever, purpura, and acroparathesias. 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, acroparathesias, 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 and transoesophageal echocardiography detected cardiomegaly and mitral vegetations on the tricuspid valve; in 70–90% of patients with CV a triggering role of hepatitis C virus (HCV) has been suggested.\(^3\) We report the case of two patients who showed a typical CV with severe neurological involvement as the presenting manifestation of underlying IE.

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 are combined with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the presentation can mean a misdiagnosis; moreover, steroid treatment can contribute to masking and worsening of the underlying infectious disorder.1

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 viruses6; the presence of particularly severe skin purpura; and the presence of neuropathy 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. It is one of the most common clinical manifestations in patients with CV,14 whereas the aetiopathogenesis of which is still unclear. In a considerable number of patients with IE negative blood cultures have also been recorded,15 often when Gram negative bacteria are involved.1

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 disease of which is still largely unknown, infecting both children and adults. Associated diseases and etiologic factors in 303 patients. Medicine (Baltimore) 1998; 77: 403-8.11

ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmatic antibodies (ANCA) positivity—namely, hyalurazine, penicillamine, allopurinol, and propylthiouracil17.

Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis,17 other antithyroid drugs, such as carbimazole and thiamazole, have been linked. Furthermore, ANCA positivity has been described in the course of Graves’ disease without vasculitis.18

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease.21

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 immunofluorescence (IF) on ethanol fixed granulocytes, as described elsewhere.20 Staining patterns were described as cANCA, when a diffuse granular cytoplasmatic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed, and as ANCA when a distinct, homogeneous, non-granular cytoplasmatic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere.21 Hospital Universitari Germans Trias i Pujol is a 553 bed hospital situated on the outskirts of Barcelona. 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 1/25 60. The immunofluorescence staining pattern was as follows: nine (26%) pANCA, seven (20%) cANCA, and five (14%) cANCA. ELISA was positive in just one case (for MPO)—in the patient with an IF titre of 25 60.

Our results are very similar to those of Afdetra et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with Graves’ disease.21 The IIF staining pattern was cANCA in five cases and cANCA in one case. Anti-MPO antibodies 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.

Table 1: Epidemiological, clinical, and seroimmunological 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</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>Absent</td>
</tr>
<tr>
<td>CRP (normal &lt;5 mg/l)</td>
<td>53</td>
</tr>
<tr>
<td>WBC [normal 5–10 x 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>yGlobulinaemia (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>&lt;60</td>
</tr>
<tr>
<td>Cryocrit, % [cystype]</td>
<td>0.5 (g/g-lmg)</td>
</tr>
<tr>
<td>Hepatitis virus markers*</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*HBsAg, anti-HBs, anti-HBC IgM, anti-HBC, anti-HCV by ELISA and RIBA; anti-EBV IgM, anti-HIV.
Lupus relapse after prostaglandin E, 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.1 We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E (PGE), administration, which to our knowledge has not been previously reported. A 25 year old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud’s phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy proven diffuse proliferative lupus glomerulonephritis (WHO class IV). A physical 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 hypocomplementemia (C3 0.6 g/l, C4 0.1 g/l), with normal liver, renal, and haematological parameters. Treatment with 40 mg/12 h IV PGE, 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. PGE was withdrawn and IL-10, 60 mg/day, was started with prompt improvement in the symptoms.


References
4 “Intracellular cytokine production after PGE1 stimulation in the human T helper cell type 2 (Th2) cytokines, such as IL4, in promoting and perpetuating B cell hyperactivity and autoantibody formation.” In: Anti-inflammatory agents and their potential therapeutic use in lupus. Poster presented at the American Rheumatism Association Annual Meeting, Washington, DC, 1996.

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

<table>
<thead>
<tr>
<th></th>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE</td>
<td>Basal PGE</td>
<td>Basal PGE</td>
<td></td>
</tr>
<tr>
<td>Patient 1.2</td>
<td>1.0</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Control 0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

IL2: interleukin-2, INFγ: interferon γ.
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. 1 Synovial and serum osteocalcin correlate positively. 2 In ankylosing spondylitis (AS) the serum concentration has been reported to be low 3 or normal. 4, 5 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein. 6 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. 6

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female) aged 11 (9) years; disease duration 19 (9) 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 radion treatment as prescribed by the patient’s doctor. Patients were advised not to change their drug treatment. The ESR was determined according to Westergren, the result at one hour being low or normal.? The ESR at the first measurement was ESR 16 (8, 26.5) mm/1st h, osteocalcin 26.1 (18.9, 32.7) ng/ml. Values at the first measurement were ESR 18 (8, 28) mm/1st h, serum osteocalcin 25 (20.5, 32.8) 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, 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 to 4, 6 mm/1st h) and in osteocalcin (–0.5 to +2.5 ng/ml) showed no significant correlation (r = 0.02; 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.

References


Takayasu arteritis

Takayasu arteritis is a chronic inflammatory vasculitis that occurs primarily in young women. It mainly affects the aorta and its major branches. 1 The Centre for Disease Control and Prevention has broadly defined idiopathic CD4+ T lymphocyte-topenia as a reproducible depletion of CD4 lymphocytes below 0.3×109/l in the absence of HIV infection or other known causes of immunodeficiency. 2 We report a case of Takayasu arteritis with low CD4+ T lymphopenia without evidence of HIV infection in a boy from Turkey.

A 9 year old boy was admitted with a history of dyspnoea, malaise, and cough for four months. Before admission the patient had been prescribed treatment for pneumonia. He had no history of recurrent infection until four months before his admission. There was no parental consanguinity or any immunocompromised person in his family. Physical examination showed a temperature of 36°C, pulse rate of 140 beats/min, respiratory rate of 50/min, and a blood pressure of 110/70 mm Hg. His height and weight were below the fifth centile. He had a gallop rhythm, grade 3/6 pansystolic murmur at the 4th–5th left intercostal space and hepatomegaly. A chest x-ray examination showed cardiomegaly and pulmonary oedema. The following laboratory values were obtained: haemoglobin 113 g/l packed cell volume 0.35, leucocyte count 8.3×10³/l, platelet count 371×10⁹/l, erythrocyte sedimentation rate 71 mm/1st h. Other test findings, including serum electrolytes, blood urea nitrogen, and creatinine, were all normal. Echocardiography showed a dilated cardiomyopathy associated with severe mitral and aortic insufficiency. The patient was treated for heart failure with inotropic agents and furosemide (frusemide) and improved greatly. At the fourth month of follow up a physical examination showed hypertension and decreased left radial and brachial pulses. A systolic blood pressure difference greater than 10 mm Hg between both arms appeared (right arm, 140/100 mm Hg; left arm, 110/70 mm Hg). Laboratory findings showed increased blood urea nitrogen and creatinine levels. Urine analyses disclosed microscopic haematuria and mild proteinuria. Antinuclear antibodies were positive (1/20). Protein electrophoresis showed a decreased serum albumin level, hypergammaglobulinaemia, and increased IgG, IgM, and IgA levels. Serum C3 and C4 levels were normal. HLA-B52 was negative. Table 1 shows the immunological findings of this patient. A lymphocyte proliferation test was not carried out on the patient. Enzyme linked immunosorbent assay (ELISA) and polymerase chain reaction tests for HIV-1 and HIV-2 were repeatedly negative, but we did not look for HTLV-1 and HTLV-2. Echecardiography disclosed dilatation of the thoracic aorta and stenosis of the left subclavian artery. Magnetic resonance imaging showed dilatation and irregular contour of the ascending and descending aorta, and narrowing of the abdominal aorta (fig 1). The patient underwent cardiac catheterisation and aortography. Angiographic examination showed narrowing of the left subclavian artery, dilatation of the thoracic aorta, and occlusion of the superior mesenteric and renal arteries. Moreover, the patient’s left kidney could not be visualised. Takayasu arteritis was diagnosed and the patient received prednisone treatment (2 mg/kg/day), but he died in the initial steroid treatment period owing to severe cardiac failure. Takayasu arteritis may be the third most common form of childhood vasculitis after

<table>
<thead>
<tr>
<th>Table 1 Immunological data of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocyte count (×10⁹/l)</strong></td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Igg (g/l)</td>
</tr>
<tr>
<td>IgA (mg/l)</td>
</tr>
<tr>
<td>IgM (mg/l)</td>
</tr>
<tr>
<td>CD3 (×10⁹/l)</td>
</tr>
<tr>
<td>CD4 (×10⁹/l)</td>
</tr>
<tr>
<td>CD8 (×10⁹/l)</td>
</tr>
<tr>
<td>CD19 (×10⁹/l)</td>
</tr>
<tr>
<td>CD3/CD4+CD56 (×10⁹/l)</td>
</tr>
</tbody>
</table>
CD4+ lymphopenia may cause dysgamma-globulinemia and autoimmune syndromes such as Takayasu arteritis.

S Sebnem Kilic, Ö Bostan, E Çil
Uludag University Medical Faculty, Department of Paediatrics, Göürük, Bursa 16059, Turkey

Correspondence to: Dr Sebnem Kilic; sebnemkl@uludag.edu.tr

References

Figure 1 Magnetic resonance imaging shows dilatation and irregular contour of the descending aorta and narrowing of the abdominal aorta.

Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-aorta antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.1

Low CD4+ T lymphocyte counts are rare in the absence of immunodeficiency, most commonly infection with HIV. 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 lymphocytopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4x10^7/L, to determine the natural history of their infections and lymphocytopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking.8

The investigations of cases of idiopathic depletion of CD4+ T lymphocytes indicate that they probably represent various disorders, and that in some cases, low CD4+ T lymphocyte counts may 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 hypergamma-globulinemia.9 Wiskott-Aldrich and Takayasu arteritis have been reported previously; 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

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 diplopa. The first disease manifestation had started three years before, when the patient suddenly presented with diplopia and painful periorbital and eyelid 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 after 15 days); symptoms recovered completely in two weeks. A first magnetic resonance imaging (MRI) scan of the orbit had been performed before; it was normal. Serological testing for HIV infection was negative and, additionally, the patient had no risk factor for transmission of HIV infection or recent immunosuppressive treatment.

Figure 1 Orbital MRI (T weighted image with contrast) shows increased signal and size of the right rectus lateralis muscle.

www.annrheumdis.com
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 that must include isolated oculomotor palsy in the differential diagnosis.

F Falcini, G Simonini, M Resti
Department of Paediatrics, University of Florence, Italy

R Cimaz
Paediatric Department, Via Commenda 9, 20122 Milan, Italy, Rolando.Cimaz@unimi.it

Correspondence to: Dr Cimaz

References

Sciatica 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 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypersplenism. Splenectomy 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 but no infiltration. Treatment was started with citrionate and calcium.

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 L5 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 L5; 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 sciatica, 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.

F Morcos
Hope Hospital, Salford, UK
E Smith
Birch Hill Hospital, Rochdale, UK

Correspondence to: Dr F Morcos, Ward C2, Hope Hospital, Salford M6 BH2, UK

References

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 polyoid hyperplasia with many eosinophils.

Figure 1 Sagittal MR scan of the spine showing vertebral infiltration, being most intense in L2 and L5, which is biconcave (arrows).
Cytes were 18.1 weeks of treatment. Peripheral blood leukocytes underwent a second laparotomy after three months with initial clinical improvement. However, cyclophosphamide 100 mg/day were started, owing to right upper quadrant pain. The ascitic fluid was serosanguineous with a protein concentration of 3 g/l, a leucocyte count of 1.05\times10^9/l and 10% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed a calcified atheromatous plaque. 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\times10^9/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/hr, rheumatoid factor (RF) 765 IU/ml (normal <15), and total IgE 769 IU/ml (normal <100), and serum uric acid 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 leukocytes, and hyaline and hyaline granular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 55 g/l, a leucocyte count of 1.05\times10^9/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovarian histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polypsis.

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, with initial clinical improvement. However, the abdominal pain recurred and the patient underwent a second laparotomy after three weeks of treatment. Peripheral blood leucocytes were 18.1\times10^9/l with 1% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to 435 IU/ml. Purulent fluid in the peritoneal cavity and two perforations in the ileal wall were found. Bowel histology showed wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophil infiltrates. Granulomas were not found. E coli grew from the peritoneal fluid. Intravenous metronidazole and gentamicin were started. Four days later a new perforation was suspected and a third laparotomy was done, showing a perforated necrotic small bowel plaque. A broad bowel resection was performed but the patient’s evolution was complicated with high 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 eosinophil 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 (fig 2). As far as we know, this is the first report of oophoritis due to vasculitis, and it should be promptly suspected and treated. In addition, CSS ovarian involvement, although rare, should be included in the differential diagnosis of ovary vasculitis.

**Figure 1** Ovarian eosinophilic infiltration is located in the hilum area, where eosinophilic arteritis is found (haematoxylin and eosin x25, and left lower quadrant x200).

**References**

9. FORTHCOMING EVENTS

3rd International Congress on Autoimmunity
23-24 Feb 2002, Geneva, Switzerland
Contact: Professor Yehuida Shoenfeld, 3rd International Congress on Autoimmunity, PO Box 50006, Tel Aviv 61500, Israel
Tel: 9723 514 0018
Fax: 9723 517 5674
Email: autoimm02@kenes.com

**NOTICE**

Dr Barbara Ansell CBE
A service of thanksgiving for the life and work of Dr Barbara Ansell will be held on Saturday 16 February 2002 at 11 00 am at Southwark Cathedral, London Bridge. Tickets may be obtained by sending a stamped self addressed envelope to: Memorial Service, British Society for Rheumatology, 41 Eagle Street, London WC1R 4AR. All are welcome to attend.

www.annrheumdis.com
22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
Contact: Professor F.C. Breedveld, Leiden University Medical Centre, Department of Rheumatology, PO Box 9600, 2300 RC Leiden, The Netherlands
Tel: +31 (0)71 526 3598
Fax: +31 (0)71 526 6752
Email: F.C.Breedveld@lumc.nl
Website: www.euur.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 25 places.
Contact: Ms Lisa McClair, 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@f1.ser.man.ac.uk

OMERACT VI
11–14 Apr 2002; Bali
Includes two modules: MRI and economics; and four workshops: patients’ perceptions, imaging (healing), progressive systemic sclerosis, minimally important clinical difference and osteoarthritis.
Contact: Conference Organisers Q2O, Q Swann Street, Old Isleveland, Middlesex TW7 6JR, UK; or Peter Brooks, Faculty of Health Sciences, Level 1, Edith Cavell Building, Royal Brisbane Hospital, Herston 4029, Australia
Tel: +44 (4)161 275 9553
Email: tony@q2q.co.uk or p.brooks@mailbox.uq.edu.au

26th British Society for Rheumatology XIXth AGM
23–26 Apr 2002; Brighton, UK
Contact: BSR, 41 Eagle Street, London WCIR 4TL, UK
Website: www.rheumatology.org.uk

4th EULAR Sonography Course
25–28 April 2002; Madrid, Spain
The course is entitled “Practical use of musculoskeletal ultrasonography”
Contact: Esperanzo Naredo
Email: enaredo@cremas.com
Website: www.eular.org/courses and www.sameint.it/eular

10th International Vasculitis and ANCA Workshop
25–28 Apr 2002; Cleveland, Ohio, USA
Contact: Deborah J Bork, The Cleveland Clinic Foundation, Desk A50, Center for Vasculitis Care and Research, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: 216 445 8533
Fax: 216 445 7569
Email: borkd@ccf.org
Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

International Congress: New Trends in Osteoarthritis
9–11 May 2002; Milan, Italy
Contact: Organising Secretariat, O.I.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: Amphihtiorion Congress Organising Bureau
Email: hmoutsop@med.uoa.gr
Email: congress@amphihtiorion.gr

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wyss, Executive Secretary EULAR, Witikonerstrasse 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 Behcet’s Disease
27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behcet’s Disease
Up to eight young investigator awards, each of $50, will be awarded on the basis of abstracts submitted
Contact: Professor Ch.C Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabeckstrasse 60–62, 14195 Berlin, Germany
Tel: 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 revnos@rito.no

Translational Research in Autoimmunity
21–22 Sep 2002; Pavia, Italy
Contact: Organising secretariat: eventi S.R.L., Corso Cavour, 18/20 - 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 5140077 or 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@acrerhumatology.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 Pliett 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