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 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 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’ standards for β2GPI independent aCL is not appropriate. With the use of Harris’ standards,⁴ the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined.⁵ However, Harris’ 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 independent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standards for β2GPI independent assays.

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 can 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,⁹ 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 RA 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 described 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.⁶ 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

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**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=53)</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>RA-RF positive (n=36)</td>
<td>6</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>RA-RF negative (n=17)</td>
<td>1</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; β2GPI, βglycoprotein I; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.
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 β2G1 independent aCL of IgA isotype. Interestingly, 7/11 RA sera which showed binding to β2GP1 adsorbed on a high binding plate did not recognise β2GP1 associated with cardiolipin, as already reported. In contrast, 3/9 RA sera binding β2GP1 complexed with cardiolipin did not recognise 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 from 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. Some 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.

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References

Authors’ reply
In response to the comments of Ambrozic et al we would like to make some explanation 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. The dependence of aCL on β2-GP1 (β2G1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2G1 in block- ing buffer (containing fetal calf sera or bovine sera). In our previous study 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 β2G1. This method justified the terminology of β2G1 independent aCL for sera containing aCL without anti-β2G1 antibodies. The absence of anti-β2G1 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 β2G1 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 β2G1 in the assays used for the detection of β2G1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2G1) did not react with β2G1 in the other ELISA test specifically designed to detect anti-β2G1 autoantibodies, and therefore which could detect hypothetically high titres of anti-β2G1 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 used for positive controls in every microtitation 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- genic 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 (SLE) sera reacting in a VDR test. By radioim- munosay, he showed that antibodies contained in these sera were directed against cardiolipin contained in liposomes used as a reagent of the VDR test. These reagents were constituted by lipids alone without any other cofactor such as β2G1. So, Harris’s standard can also be used to detect aCL directed only against phospholipid and not against the complex β2G1-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 β2G1 used in our assay was provided by Stago laboratories (Asnière, France) and was purified from human sera. We used sodium dodecyl sulphate-polyacrylamide gel electrophoresis and western blotting to ensu re that this purified protein was not contaminated.

For every antibody determination, aCL and anti-β2G1 autoantibodies, normal levels were established from soddies of a large number of normal subjects (blood donors) as previously described. In this study, 50 sera 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-β2G1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2G1 test were prepared from positive controls from patients with APS and were used according to previous studies.

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2G1 antibodies in normal sera of APS patients. 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 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. 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 should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate related pancytopenia. Indeed, in a community based, observational study of methotrexate use in 460 patients we found the

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perioperative period to be especially hazardous for patients with renal impairment and sepse.1,2 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 patients with renal impairment (best assessed by creatinine clearance) and in the elderly. 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.1

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.3 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 phosphate 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 1.0 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, antiendomysial, and antiglutaminase antibodies were strongly positive, and a small bowel biopsy showed almost total villous 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 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, ergocalciferol 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 her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphate 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 more case reports of coeliac disease presenting with bone pain, proximal myopathy, radiographic findings of pseudo fractures and Looser’s zones, or secondary hyperparathyroidism evident on bone scan.3 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.3 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.4 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 hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.3 Secondary hyperparathyroidism can develop if it did in this case, causing increased bone turnover. 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.5

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 antidentomysial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.5,6 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 mineral density; the greater the degree of osteopenia, the more rapid the gain.1 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.6 Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.4,5

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.6

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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 sepse, and we would not disagree with this point. The risk of surgery is increased by any coincident-
ted medical disease including renal failure and sepse 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.

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LETTERS

References

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 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 18–52) and mean disease duration of 35.8 (36.6) months (range 6–268). 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 among patients than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). There was overall a negative correlation between plasma and PBMC zinc levels (p<0.05); however, patients with RA had higher levels than controls (p<0.01) and those with active RA had higher levels than those with inactive disease (p<0.01).

There was a negative correlation between plasma and PBMC copper levels (p<0.05).

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There was a negative correlation between plasma and PBMC copper levels (p<0.05).

References


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

The relevance of monoclonal gammopathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gammopathy 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 is higher 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 immunocomplexological 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 reduced 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 right hand became necrotic. Angiography showed normal vessels. Immune electrophoresis showed the presence of 8 g/l of an M component (IgGκ). An assay for the detection of cryoglobulinaemia was positive. Luminol-enhanced imaging showed normal plasma viscosity; antinuclear antibodies could not be detected and neither could rheumatoid factor. Complement components showed decreas- ed C4 levels (461/461/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 no evidence for vasculitis, but thornus formation was detected in one artery. A diagnosis of multiple myeloma was ruled out by extensive laboratory examination.

Treatment was started with prednisons 60 mg daily, chlorambucil 8 mg daily until the M component concentration reached a plateau. During this treatment the skin lesions on his foot disappeared and his finger became necrotic The M component decreased to 5 g/l. After almost a year of follow up he is still free of complaints.

Patient B was a 60 year old man who was admitted to our hospital in January 2000 with arthritis of the small joints and severe Raynaud’s phenomenon of his ears, which affected him so severely that he could not leave his house. Furthermore, he felt short of breath when breathing cold air. Physical examination showed purpura skin lesions on both helices of his ears. A paraprotein was detected with an M component of 4 g/l. The presence of a cryoglobulinaemia was shown, which consisted exclusively of the M component. Further laboratory examination showed very low levels of the complement component C1q < 151E/ml (normal 81–128), C3 1.42 g/l (normal 0.9–1.8), and C4 300 mg/l (normal 90–190). Virus serology was positive for cytomegalovirus and negative for hepatitis A, B, and C. Plasma viscosity was normal. No evidence for multiple myeloma and lymphoma was obtained. A skin biopsy of the non-affected skin showed only a slight perivascular infiltrate, and no evidence for a necrotising vasculitis was seen. He 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. Her legs were cold and very painful. Angiography showed normal vessels, which strongly suggested vasculitis of the end arterial vessels of her feet.

Laboratory examination showed a paraprotein (4 g/l) combined with a cryoglobulinaemia type 1 (IgGκ). Other laboratory examinations showed no abnormalities. Virus serology showed the presence of a cryoglobulinaemia. 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 cryoglobulin was re- duced, 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 malignant 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.

References


Cryoglobulinaemic 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 cryoglobulinaemic vasculitis (CV) associated with IE have seldom been described. CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and comple- ment; 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, paraesthesiaes, and pseuodoaxial gait. Her past clinical history was unremarkable except for a prosthetic implant of the left hip four years previously. Table 1 shows the main clinicoserological features. Repeated blood cultures were negative. Neurological examination showed abnormal tactile sensation on the feet and legs; mild ideomotor slowing down; shaky movements; and unsteady gait. An electro- physiologically study recorded a moderate sensorimotor peripheral neuropathy, while chest x-ray examination, abdominal echogra- phy, and echocardiography were normal. Cutaneous purpura biopsy disclosed a leukocy- tocytovasculasitis. Truncoencaphalic magnetic resonance imaging showed a 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. One month of treatment. Necropsy disclosed coarse endocardial vegetations on the left side valves infected by *Kangella*.

Case 2

In January 1999 a 75 year old woman with no risk factors for infections presented with fever, purpura, and acroparaesthesias. 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, arthralgias, acroparaesthesias. Table 1 and related disorders. Int J Clin Lab Res 1992;21:288–91.

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 in our patients, together with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the fatal outcome. Previous reports (Medline) showed that the association of IE with “asymptomatic” cryoglobulinaemia 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 infections, or both. However, the possibility that IE represented a complication of CV was 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 transesophageal echocardiography.

### References


### ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hyaluronic acid, penicillamine, allopurinol, and propylthiouracil. Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis, 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.

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease. The diagnosis of the disease was based on typical signs and symptoms of hyperthyroidism, raised serum triiodothyronine and thyroxine, 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. Staining patterns were described as cANCA, when a diffuse granular cytoplasmic staining with central accentuation was seen, as pANCA, when the perinuclear pattern was observed, and as xANCA when a distinct, homogeneous, non-granular cytoplasmic staining pattern was seen. Autobodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere. Hospital Universitari Germans Trias i Pujol is a 533 bed hospital situated on the outskirts of Barcel- 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 Afliter et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with Graves’ disease. The IIF staining pattern was AINCA in five cases and cANCA in one case. Anti-MPO antibo-}

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease duration (weeks)</th>
<th>Purpura</th>
<th>Weakness</th>
<th>Arthritis</th>
<th>Hepatitis</th>
<th>Neutropathy</th>
<th>Neurological involvement</th>
<th>Cardiac symptoms</th>
<th>ESR (mm/1 h)</th>
<th>CRP (normal &lt;5 mg/l)</th>
<th>WBC (normal 5–10 x 10^9/l)</th>
<th>Neutrophils (%)</th>
<th>Lymphocytes (%)</th>
<th>γGlutamyltranspeptidase (g/l)</th>
<th>RF (normal &lt;20 IU/ml)</th>
<th>C3 (normal 50–100 mg/l)</th>
<th>C4 (normal 200–550 mg/l)</th>
<th>Cryocrit, % [cryo-type]</th>
<th>Hepatitis virus markers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>63</td>
<td>7</td>
<td>Yes</td>
<td>Severe</td>
<td>Recurrent</td>
<td>Absent</td>
<td>Absent</td>
<td>Peripheral + central</td>
<td>Absent</td>
<td>81</td>
<td>89 000</td>
<td>81 000</td>
<td>10</td>
<td>19.5</td>
<td>575</td>
<td>33</td>
<td>930</td>
<td>600</td>
<td>0.5 [IgG-IgM]</td>
<td>Negative</td>
</tr>
<tr>
<td>Patient 2</td>
<td>75</td>
<td>9</td>
<td>No</td>
<td>Mild-moderate</td>
<td>Constant</td>
<td>Absent</td>
<td>Absent</td>
<td>Peripheral</td>
<td>Absent</td>
<td>83</td>
<td>32 600</td>
<td>83 600</td>
<td>87</td>
<td>9.5</td>
<td>19.5</td>
<td>33</td>
<td>77</td>
<td>32</td>
<td>0.5 [IgG-IgM]</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*HBsAg, anti-HBs, anti-HbcIgM, 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. Recombinant cytokines demonstrate 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 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 proving 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 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 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 anemia, 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 the patient received dexamethasone, 60 mg/day, was started with prompt improvement in the symptoms.

We investigated the possibility that PGE, 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 PGE, stimuli (10 ng/ml) was determined by flow cytometry using anti-cytokine conjugates in combination with surface anti-CD3 (Pharminigen, San Diego, CA), as previously described. The test performed eight months after the PGE, treatment showed a dramatic rise in interleukin 4 (IL4) 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 Th 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, in some studies it has been suggested that PGE, alters the Th1/Th2 balance of T cells to a dominant Th2 response. We suggest that the rise in IL4 production induced by the PGE, as shown 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.

References


Table 1: Intracellular cytokine production after PGE 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>Cytokine</th>
<th>Basal PGE</th>
<th>PGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>INFγ</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>IL4</td>
<td>1.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

IL, interleukin; 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. Serum and synovial osteocalcin correlate positively. In ankylosing spondylitis (AS) the serum concentration of osteocalcin 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; mean age 41 years; disease duration 11 years; 61 patients were under 50 years old) serum osteocalcin was determined. Venous blood was taken at the start of the study and at the end of therapy with low dose steroids. Serum osteocalcin was measured in one batch with a commercially available test kit (IRMA, Biocis, Vienna; −18°C until further analysis. Osteocalcin was determined in serum samples from patients with active ankylosing spondylitis and in patients with inactive disease. In addition, 20 patients with rheumatoid arthritis were included in this study.

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.

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**Table 1 Immunological data of the patient**

<table>
<thead>
<tr>
<th>Values</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte 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>(8-19.4)</td>
</tr>
<tr>
<td>IgA (mg/l)</td>
<td>6290</td>
<td>(620-3980)</td>
</tr>
<tr>
<td>IgM (mg/l)</td>
<td>531</td>
<td>(240-3990)</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>0.2-1.6</td>
</tr>
<tr>
<td>CD3/CD16+CD56 (×10^9/l)</td>
<td>0.2</td>
<td>0.1-0.9</td>
</tr>
</tbody>
</table>

---


12 Takayasu arteritis: a chronic inflammatory vasculitis that occurs primarily in young women. It occurs worldwide, with greatest prevalence in Asian people. It mainly affects the aorta and its major branches.

13 Takayasu arteritis was diagnosed and 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, IgA, and IgM. 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. Echocardiography disclosed dilatation of the thoracic aorta and stenosis of the left subclavian artery. Magnetic resonance imaging showed dilatation of the left subclavian artery 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.
CD4+ lymphopenia may cause dysgammaglobulinemia and autoimmunity syndromes such as Takayasu arteritis.

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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.7

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 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 lymphopenopatía. Two recent preliminary reports suggest a decrease in the titre of virus neutralizing antibody in patients with idiopathic CD4+ T lymphopenia—an analysis of five patients with unexplained opportunistic infections. N Engl J Med 1993; 328: 384–7.

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 and eyelid oedema. Limited abdution 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 shown first degree exophthalmus of the right eye and oedema and thickening of the right rectus lateralis 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 one 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, creatine 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, anticardiolipin, antinuclear factor) 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. Electromyography 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 insertion 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.8 Orbital muscle infection 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 muscle.
Hodgkin’s lymphoma is rare. System and vertebrae by low grade non-steroidal anti-inflammatory drugs 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.

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References

Sciatica or spinal lymphoma

The involvement of the central nervous system and vertebrae by low grade non-Hodgkin’s lymphoma is rare.1 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 buttck, 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 plantar were down going, both plantar were down going, 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. 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 and no infiltration. Treatment was started with etidronate 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.

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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 unusual2 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 polypoid hyperplasia with many eosinophils.
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 18.1 × 10^9/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed calcified cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovarium. A cholecystectomy and right aneuxectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.90 × 10^9/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal <20), and total IgE 769 IU/ml (normal <100), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antinuropoetin 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 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovarium histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyposis.1

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 × 10^9/l with 1% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to 4.35 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 eosinophilic 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 29–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described,1,2,3 the last of these being responsible for up to 10% of the CSS deaths.4 Acalculous cholecystitis, although very rare, may be the first and sometimes the unique manifestation of the CSS.1,5 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 oварium 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 involve- ment in the CSS,5 but has only been confirmed in one case so far.7

The poor response to steroids and cyclophosphamide is striking. Despite the reduction of the peripheral eosinophila and ESR there was widespread eosinophilic bowel infiltration and vascular fibrinoid necrosis in the laparotomy samples. The evolution of the disease in our patient was catastrophic, especially as she had only one of the five Guillevin CSS mortality associated factors — namely, gastrointestinal involvement.6

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 ovary vasculitis.

References
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International Congress: New Trends in Osteoarthritis
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10F World Congress on Osteoporosis
10–14 May 2002; Lisbon, Portugal
Contact: IOF Secretariat, 71 cours Albert Thomas, F-69003 Lyon, France
Tel: +33 4 72 91 41 77
Fax: +33 4 72 36 90 52
Email: info@iof Lyon.org
Website: www.osteofound.org

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

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wyss, Executive Secretary EULAR, Wilkonserstrasse 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 $500, 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, Fachbereich Bull, 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 27298
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, 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; Turin, Italy
Deadline for abstracts 1 April 2002
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kones International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 5140018
Fax: 972 3 5140077 or 972 3 5172484
Email: aps@kones.com
Website: www.kones.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 290, Atlanta, Georgia 30045–4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@acr.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, Boul de 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

www.anrnreumdis.com
ANCA antibodies in Graves' disease

M Gumà, A Olivé, M Juan and I Salinas

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