Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled "Antiphospholipid antibodies and RA: presence of $\beta$GPI 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 term "anticardiolipin antibodies" was somewhat misleading. The term was introduced and abbreviated as "aCL", a group of antibodies detected in many conditions, but the $\beta$ glycoprotein I ($\beta$GPI) dependence of the aCL was not defined, even though the authors focused on $\beta$GPI independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines both $\beta$GPI dependent and $\beta$GPI independent antibodies.

There were some potential methodological errors in determining $\beta$GPI independent aCL. It was shown that antibodies against $\beta$GPI (anti-$\beta$GPI) from patients with the antiphospholipid syndrome (APS) have the ability to bind $\beta$GPI in complexes with cardiolipin only if the $\beta$GPI concentration in solution is high enough. The threshold concentration of $\beta$GPI was found to be just about 2 $\mu$g/ml, because no binding of anti-$\beta$GPI was seen when serum samples were diluted 1:200 or more.2 As the physiological concentration of $\beta$GPI in human serum is approximately 200 $\mu$g/ml, the threshold binding concentration is reached at a serum dilution of 1:100. In the presence of a relatively high concentration of endogenous $\beta$GPI, the statement that antibodies detected by this method are exclusively $\beta$GPI independent is unjustified, as the sera containing high titres of anti-$\beta$GPI 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 $\beta$GPI independent aCL is not appropriate. With the use of Harris's standards,3 the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined.4 However, Harris's standards were designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominately, $\beta$GPI dependent aCL. $\beta$GPI independent aCL were not defined in those standards and they were not meant as standards for $\beta$GPI independent assays.

The interpretation of $\beta$GPI dependent aCL ELISA as a method to detect $\beta$GPI dependent aCL may not be valid in all cases. It was shown that not all anti-$\beta$GPI binding $\beta$GPI adsorbed on polystyrene high binding plates also recognise $\beta$GPI associated with cardiolipin. We reported this binding pattern for anti-$\beta$GPI in children with atopic dermatitis,5 and the same was shown also for some patients with autoimmune diseases, including APS.6

The method for purification of $\beta$GPI was not described. Because the authors focused on patients with rheumatoid arthritis (RA), it should be ensured that immunoglobulins for $\beta$GPI preparation. If this purification step was not carried out, traces of immunoglobulins in the $\beta$GPI preparation might have yielded positive results for sera containing high titres of rheumatoid factor (RF). In fact, all sera containing IgM anti-$\beta$GPI 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 $\beta$GPI independent aCL and for anti-$\beta$GPI. We recently compared the sensitivity of anti-$\beta$GPI 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.7 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,8 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-$\beta$GPI, $\beta$GPI dependent aCL, and $\beta$GPI independent aCL. The cut off values for anti-$\beta$GPI 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 sera for both $\beta$GPI dependent and $\beta$GPI independent aCL. For the anti-$\beta$GPI determination, we used affinity purified $\beta$GPI adsorbed on Costar high binding plates as previously described.10 The $\beta$GPI preparation did not contain any immunoglobulins. $\beta$GPI independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for $\beta$GPI dependent aCL on the same plate by adding $\beta$GPI in parallel duplicate wells. The final concentration of $\beta$GPI was 10 $\mu$g/ml. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of $\beta$GPI. For the final determination of $\beta$GPI dependent binding, the values obtained in wells without $\beta$GPI were subtracted from the values measured in wells with added $\beta$GPI. The patients' histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the $\chi^2$ 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-$\beta$GPI, $\beta$GPI dependent aCL, and $\beta$GPI independent aCL was higher in patients with RA than in controls, but the difference was significant only for anti-$\beta$GPI. There were no differences in the frequency of $\beta$GPI 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.9 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,8 which is only one of the several published estimations of aPL in healthy subjects.

Table 1 Frequency of anti-$\beta$GPI, $\beta$GPI dependent aCL, and $\beta$GPI independent aCL in patients with rheumatoid arthritis (positive or negative for RF) and normal controls

<table>
<thead>
<tr>
<th></th>
<th>Anti-$\beta$GPI</th>
<th>$\beta$GPI dependent aCL</th>
<th>$\beta$GPI independent aCL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>Any Ig</td>
</tr>
<tr>
<td>No of positive samples:</td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>NHS (n=53*)</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>RA (n=53)</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA - RF (n=30)</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA - RF (n=17)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; $\beta$GPI, $\beta$ glycoprotein I; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.

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any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2GP1 and β2GP1 dependent aCL of IgA isotype. Interestingly, 8/11 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 to 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 of 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.

The patients with RA may have anti-β2GP1 and β2GP1 independent aCL, which might be associated with the signs of APS. The importance of distinguishing β2GP1 independent aCL in APS has not been fully clarified. It seems 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 comments 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 serum by the dependence of aCL on β2 glycoprotein I (β2GP1). aCL is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2GP1 in blocking buffer (containing fetal calf sera or bovine serum). In our previous study, a positive 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 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 concentration of endogenous 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 β2GP1 in the other ELISA test specifically designed to detect anti-β2GP1 autoantibodies, and therefore which could detect hypothetically high titer 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 were used as positive controls in every microtitration plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera. The antiphospholipid antibodies, including aCL, are directed against several anti-genenic 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, in sera reacting in a VDRL test. By radioimmunoassay and association with thrombosis in systemic lupus erythematous. Lancet 1983;381:1211–14.


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 pancyclopaenia. Indeed, in a community-based, observational study of methotrexate use in 460 patients we found the

References

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periooperative period to be especially hazardous for patients with renal impairment and sepsis. Two subjects developed pancytopenia under these conditions, one of whom died.

Although all consecutive patients were included in the study by Grennan et al., it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made about the prevalence of 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.  

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References

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

lets

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 pain was 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, antiantidiomysial, 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 0.653 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 phosphatase reduced to 374 U/l. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm² (mean level for young adult women), and the neck of the femur by 39% to 0.878 g/cm² (0.8 SD below the mean). She had also gained more than 7 kg in weight, and repeat gastroscopy and duodenal biopsy were normal.

Osteomalacia is now an uncommon disease, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965, 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. 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 hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.

Secondary hyperparathyroidism can develop, as 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.

Early diagnosis of coeliac disease is important because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determination of anti-glutaminase and anti-endomysial 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 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. 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 menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.

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 hormone replacement therapy including vitamin D may lead to rapid and effective recovery.

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

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

Patients attending the rheumatology clinic at our institute and satisfying the American College of Rheumatology (formerly American Rheumatism Association) criteria for the diagnosis of RA were studied. Patients were categorised as either active or inactive RA. All patients classified as active RA had at least three of the following: morning stiffness for more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. Both plasma and lyed 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 55.8 (36.6) months (range 6–168). Twenty patients had inactive and 19 patients active disease, respectively. Twenty two healthy controls (14 women), well matched for age (mean age 34.2 (6.2) years, range 20–56) with the two patient groups, were studied at the same time. Both patients and controls were of middle socioeconomic status. Table 1 shows the plasma and PBMC levels of Zn and Cu. Our results are in agreement with earlier studies which showed that plasma Zn levels are significantly lower and plasma Cu levels significantly higher in patients with active RA. Additionally, it is shown here that PBMC levels of these elements have an inverse relation with plasma levels.

With acute inflammation, the acute phase response may move Zn into the liver and the reduced plasma concentration may not be indicative of overall deficiency. Possibly, also, PBMCs may be an additional site to which Zn is moved during inflammatory states. The average disease duration of patients with active disease was more than 54 months. In such a long process it is unclear whether chronic cytokine release, as is seen in RA, causes a shift of Zn from one compartment to another or if there is a true Zn depletion. Significantly, there was no correlation between age or duration of disease and plasma or PBMC levels of Zn.

The finding of raised Cu levels in the plasma is to be expected because of a concomitant rise of caeruloplasmin, which is an acute phase reactant. The reduced levels in PBMCs may signify a movement of Cu from PBMCs to the liver where it is absorbed and attached to caeruloplasmin. Thus the findings of plasma and PBMC Cu levels may merely be a reflection of an acute phase response, and the alterations may be due to increased hepatic synthesis of caeruloplasmin.

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

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

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References


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

The relevance of monoclonal gamopathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gamopathy or

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**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 Zn (µg/l)*</td>
<td>687 (467)</td>
<td>982 (254)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>PBMC Zn (µg/10^6 cells)**</td>
<td>135.2 (28.6)</td>
<td>108.3 (38.4)</td>
<td>121.4 (34.4)</td>
<td>984 (16.4)</td>
</tr>
<tr>
<td>Plasma copper (µg/l)†</td>
<td>1646 (357)</td>
<td>1016 (296)</td>
<td>1426 (324)</td>
<td>946 (446)</td>
</tr>
<tr>
<td>PBMC copper (µg/10^6 cells)**</td>
<td>50.9 (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 second line drug with plasma or PBMC levels of Zn and Cu.

*Overall 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).†Towerrall levels were significantly higher than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05).‡There was an overall negative correlation between plasma and PBMC zinc levels (p<0.05).‡Towerrall, patients with RA higher levels than controls (p<0.01) and those with active RA higher levels than those with inactive disease (p<0.01); †Towerrall, patients with RA had higher levels than controls (p<0.01) and those with active RA higher than those with inactive disease (p<0.01). There was a negative correlation between plasma and PBMC copper levels (p<0.05).
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 immunological properties, paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the so-called cryoglobulins. When cryoglobulins are detected in the serum of a patient, this finding is usually associated with the coexistence of paraproteins. Recently, three patients with a clinical picture of a necrotising vasculitis associated with an essential cryoglobulinaemia (type 1) were admitted to our department.

The causative relationship between the cryoglobulinaemia and the clinical symptoms was 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 left ear became necrotic. Angiography showed normal arteries. Immune electrophoresis showed the presence of 8 g/l of an M component (IgGκ). Further laboratory examination showed the presence of cryoglobulinaemia, detected with an M component of 4 g/l. The patient had Raynaud’s phenomenon and in different disease entities like amyloido-

The upper part of his left hand was taken up by the cold until he could not leave his house. Furthermore, he felt short of breath when breathing cold air. Physical examination showed purpura skin lesions on his foot the necrosis began to demarcate to the upper part of her feet. 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, paraproteins have seldom been described and no underlying disease is present, neither could rheumatoid factor. Complement components showed decreased C3 (1.42 g/l (normal 0.9–1.8)) and C4 (300 mg/l (normal 0–400)), abnormal tactile sensation in the limbs and legs; mild idiomotor slowing down; shaky movements; and unsteady gait.

In our patients we were able to show that the cryoglobulins were formed by the monoclonal immunoglobulin. When the serum concentration of the cryoglobulins 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 symptoms are present.

References

as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the aetiopathogenesis of CV symptoms was together with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the fatal outcome. Previous reports (Medline) show that the association of IE with "asymptomatic" 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 the patients we can reasonably exclude the possibility that IE represented a complication of the CV. In over 300 of our patients with CV, bacterial manifestations have rarely been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in our two patients had quite unusual clinical and virological characteristics: absence of HCV or other hepatotropic viruses; the presence of particularly severe cryoglobulinaemia; in one case associated with peripheral neuropathy, in one case associated with hepatitis; and with fever unresponsive to steroids it is strongly recommended that other less common, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinicimicrobiological evaluation, including transeosophageal echocardiography.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>Disease duration (weeks)</td>
<td>7</td>
<td>9</td>
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<tr>
<td>Purpura</td>
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<tr>
<td>Weakness</td>
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<td>ESR (mm/1st h)</td>
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<td>CRP (normal &lt;5 mg/l)</td>
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<td>WBC (normal 5–10 × 10^9/l)</td>
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<td>83,600</td>
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<td>Neutrophils (%)</td>
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<td>Lymphocytes (%)</td>
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<td>γ-Globulinaemia (g/l)</td>
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<td>C3 (normal 500–1200 mg/l)</td>
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<td>C4 (normal 200–550 mg/l)</td>
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*HBSAg, anti-HBs, anti-HBClgM, anti-HBC, anti-HCV by ELISA and RIBA; anti-EBV lgM, anti-HIV.

References


ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hydralazine, 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. 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. Staining patterns were described as cANCA, when a diffuse granular cytoplasmic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed, and as ANCA when a distinct, homogeneous, non-granular cytoplasmic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme-linked immunosorbent assay (ELISA; Ortho-Centec) as described elsewhere. 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 (IIF) 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%) cANCA, and five (14%) cANCA. ELISA was positive in just one case (for MPO)—in the patient with an IFI titre of 1/2560.

Our results are very similar to those of Alettria et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with Graves’ disease. The IIF staining pattern was ANCA 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.
Human MPO and human thyroid peroxidase (TPO) share global similarities which indicate that MPO and TPO are members of the same gene family. Therefore, it seems conceivable that MPO autoantibodies may cross react with TPO. Findings suggesting such a relationship were reported by Haapala et al. who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and who found antibodies against both TPO and the Society for Rheumatology.

This study was sponsored by a grant from the Catt Institute. There is a need to determine the autoantibody role of ANCA antibodies in Graves’ disease, the precise relation between ANCA and antithyroid drugs and, lastly, the antigens which are responsible for the ANCA positivity.

ANCA positivity in Graves’ disease may be attributable to either antithyroid drugs (thiamazole or propylthiouracil) or to the disease itself.

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Acknowledgment
This study was sponsored by a grant from the Catalan Society for Rheumatology.

References

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 emphasize 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 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 oral prednisone, 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 (Pharmingen, 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 I).

It has been suggested that cytokines have an important role in the immune dysregulation seen in lupus prone mice and in patients with SLE. Increasing evidence supports a role for T helper cell type 2 (Th2) cytokines, such as IL4, in promoting and perpetuating B cell hyperactivity and autoantibody formation. A change in the proportion of Th2 cytokines might be associated with the polyclonal B cell activation seen in SLE. Restoration of Th1 and Th2 cytokines to levels similar to those seen in healthy mice results in amelioration of the clinical manifestations of an already established experimental SLE.

On the other hand, 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.

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<table>
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IL, interleukin; INFN, interferon γ.

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.
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 low3 or normal.4 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.5 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; age at diagnosis 11 years; disease duration 19 years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, occupational therapy, electrotherapy, underwater exercises, and raiflown treatment as prescribed by the patient's doctor. Patients were advised not to change their drug treatment. The ESR was determined according to the Westergren method. The result at one point was used for calculation. Serum was frozen at −18°C until further analysis. Osteocalcin was measured in one batch with a commercially available kit (IRMA, Biosit, Vienna; normal range according to the manufacturer 7.5–31.5 ng/ml in men, 3.7–31.7 ng/ml in women). Results are given as median (25th, 75th centile). The Mann-Whitney rank sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 19 (18, 28) mm/1st h, serum osteocalcin 25 (20.5, 52.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/1st h, osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR and osteocalcin at the first examination did not correlate significantly (r=0.07; p=0.5). The changes in ESR (1–4, 6 mm/1st h) and changes in osteocalcin (−0.5 to +2.6 ng/ml) showed a significant correlation (r=0.28; p<0.01).

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

References


Takayasu arteritis

Takayasu arteritis is a chronic inflammatory vasculitis that occurs primarily in young women. It occurs world wide, with greatest prevalence in Asian people. It mainly affects the aorta and its major branches.7 The Centers for Disease Control and Prevention Prevention have broadly defined idiopathic CD4+ T lymphocytopenia as a reproducible depletion of CD4 lymphocytes below 0.3×10^9/l in the absence of HIV infection or other known causes of lymphocytopenia.8 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 30/min, and a blood pressure of 110/70 mm Hg. His weight and height 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 8.3×10^9/l, platelet count 371×10^9/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, hypergammaglobulinemia, and increased IgG, IgM and C3 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 and irregular contour of the thoracic 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 Kawasaki disease.
CD4+ lymphopenia may cause dysgamma-globulinaemia and autoimmunity syndromes such as Takayasu arteritis.

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References

Recurrent orbital pain and diplopia in a 12 year old boy

A previously healthy 12 year old boy was referred to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia. The first episode of pain 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 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 well-being, 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, anticycardiolipin, antinuclear antigen, antinuclear antistreptolysin O antibodies) were undetectable. Other markers that are considered measures of disease activity in juvenile inflammatory myopathies were evaluated: factor VIII related antigen levels were raised, while neopterin levels and the number of circulating B lymphocytes (CD19 positive cells) were normal. Electrocardiography and two dimensional echocardiography excluded a concurrent myocarditis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (ScI), Crohn's disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extrinsic and of the right medial rectus muscles. Electromyography showed increased insertional activity, fibrillations, and positive sharp waves. Ocular myositis was diagnosed. The oral prednisone dose was raised to 30 mg/day and rapidly tapered after improvement of signs and symptoms. In November 2000, cyclosporin (3 mg/kg/day) was introduced; no relapse of the oculomotor diplopia 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 oral myositis, a condition that is rare in adults and even rarer in children.10 Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, Scl, giant cell myocarditis, and Crohn's disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease, ocular myopathies, such as mitochondrial disorders and ocular dystrophies; and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinuses are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extracocular muscle compartments. The most common cause of this condition is idiopathic orbital inflammation (Inflamed eye disease; IME). The two morphological patterns of IME are IME classically defined and orbital pseudotumour (OP). The clinical presentation of these two entities is similar, but the differential diagnosis is based on evaluation of different imaging features. The clinical presentation of IME is characterized by acute onset, pain, and proptosis. The differential diagnosis of IME includes orbital cellulitis, neoplasms, arteriovenous malformations, and cavernous sinuses.

**Figure 1** Orbital MRI (T1 weighted image with contrast) that shows increased signal and size of the right rectus lateralis muscle.
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 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 ocular myositis 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. 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 restriction of movement with tenderness of lower lumbar lymphadenopathy. He had restricted back movement (MRI) scan showed collapse of T7 and wedging of T4, with evidence of 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 unusual and normally resolve after immuno-suppressive 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.

Abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotopic scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes.

In a previous 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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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 1×10^9/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed acalculous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovarium. A cholecystectomy and right aneuxotomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.89×10^9/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal <80), and total IgG 1769 IU/ml (normal <100), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antineutrophil cytoplasmic antibody values were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaline and hyaline-fragmentary 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 1.05×10^9/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovary histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyposis.

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 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 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, 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 in the CSS, but has only been confirmed in one case so far.

The poor response to steroids and cyclophosphamide is striking. Despite the reduction of the peripheral eosinophilia 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 Guillemin CSS mortality associated factors—namely, gastrointestinal involvement.

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

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

**References**


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

M Wong, J Scally, K Watson and J Best

Ann Rheum Dis 2002 61: 87-88
doi: 10.1136/ard.61.1.87

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