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).2,3—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. As the physiological concentration of β₂GPI in human serum is approximately 200 µg/ml, the threshold binding concentration is reached at a serum dilution of 1:100. In the presence of a relatively high concentration of endogenous β₂GPI, the statement that antibodies detected by this method are exclusively β₂GPI independent is unjustified, as the sera containing high titres of anti-β₂GPI might have yielded positive results by the method described in the letter.

The definition of antibody units in the letter is not clear and using Harris’s standards for β₂GPI independent aCL is not appropriate. With the use of Harris’s standards,4 the units should be abbreviated as GPl (for IgG) and MPl (for IgM) as previously defined.5 However, Harris’s standards were designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominantly, β₂GPI independent aCL. The β₂GPI independent aCL were not defined in those standards and they were not meant as standards for β₂GPI independent assays.

The interpretation of anti-β₂GPI ELISA as a method to detect β₂GPI dependent aCL may not be valid in all cases. It was shown that not all anti-β₂GPI binding β₂GPI adsorbed on polystyrene high binding plates also recognize β₂GPI associated with cardiolipin. We reported this binding pattern for anti-β₂GPI in children with atopic dermatitis,6 and the same was shown also for some patients with autoimmune diseases, including APS.7

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

The method for determining cut-off values was not explained and the number of normal human sera (NHS) included in the study as negative controls was not given. From the data presented in the letter, one may conclude that the cut-off values were arbitrarily set at 20 units both for IgG and IgM isotypes of β₂GPI independent aCL and for anti-β₂GPI. We recently compared the sensitivity of anti-β₂GPI ELISA and classical aCL ELISA. The results showed great differences between their sensitivities and therefore also between the cut-off values calibrated by the same standards.8 In addition, the authors did not report the proportion of NHS positive for each assay and the values of positive samples compared with patients with RA. Instead, they just referred to one study,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 ARA criteria for RA and 53 NHS as negative controls. The samples were tested for anti-β₂GPI, β₂GPI dependent aCL, and β₂GPI independent aCL. The assays were calibrated with β₂GPI dependent monoclonal aCL (IgG and IgM anti-β₂GPI ELISA and β₂GPI dependent aCL ELISA) and positive in-house standards (all IgA assays and β₂GPI independent aCL). The cut-off values for anti-β₂GPI were set as described9 by calculating the mean + 2 SD of logarithms of absorbance values for NHS and the 95th centile value of 32 NHS sera 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. The β₂GPI dependent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for β₂GPI dependent aCL on the same plate by adding β₂GPI in parallel duplicate wells. The final concentration of β₂GPI was 10 µg/ml. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β₂GPI. For the final determination of β₂GPI dependent binding, the values obtained in wells without β₂GPI were subtracted from the values measured in wells with added β₂GPI. The patients’ histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the χ² test where appropriate.

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

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

<table>
<thead>
<tr>
<th>No of positive samples:</th>
<th>Anti-β₂GPI*</th>
<th>β₂GPI dependent aCL</th>
<th>β₂GPI independent aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgA</td>
</tr>
<tr>
<td>NHS (n=53*, n=32†)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>RA (n=53)</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>RA - RF (n=36)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RA - RF - n=17)</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

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

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PostScript

MATTERS ARISING

Antiphospholipid antibodies and rheumatoid arthritis

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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-β 2GP1 and β 2GP1 dependent aCL of IgA isotype. Interestingly, 5/11 RA sera which showed binding to β 2GP1 adsorbed on a high binding plate did not recognise β 2GP1 associated with cardiolipin, as already reported. 1 In contrast, 3/9 RA sera binding β 2GP1 complexed with cardiolipin did not recognise β 2GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β 2GP1 in RA, which may differ in fine specificity to β 2GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β 2GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β 2GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β 2GP1 (10 μg/ml) lowered the binding of β 2GP1 independent aCL, by about 50%, most probably owing to the competition between β 2GP1 independent aCL and β 2GP1 for the same binding sites on cardiolipin. Patients with RA may have anti-β 2GP1 and β 2GP1 dependent aCL, which might be associated with the signs of APS. The importance of distinguishing β 2GP1 independent aCL has not been fully clarified. It seems probable that β 2GP1 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 add information to the data published earlier in the Annals. 3

The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera of patients with the dependence of aCL on β 2 glycoprotein I (β 2GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β 2GP1 in blocking buffer (containing fetal calf sera or bovine sera). In our previous study the 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 β 2GP1. This method justified the terminology of β 2GP1 independent aCL for sera containing aCL without anti-β 2GP1 antibodies. The absence of anti-β 2GP1 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 β 2GP1 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 β 2GP1 in the assays used for the detection of β 2GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β 2GP1) did not react with β 2GP1 in the other ELISA test specifically designed to detect anti-β 2GP1 autoantibodies, and therefore which could detect hypothetically high titer of anti-β 2GP1 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 regarded as positive controls in every microtiter plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera. 5 The antiphospholipid antibodies, including aCL, are directed against several anti-cardiolipin autoantibodies. Among them, some epitopes are located on the cardiolipin alone. These data were described by Harris when aCL were first characterised in systemic lupus erythematosus sera reacting in a VDRL test. By radioimmunoassay, he showed that antibodies contained in these sera were directed against cardiolipin contained in liposomes used as a reagent of the VDRL test. 6 Two of these reagents were constituted by lipids alone without any other cofactor such as β 2GP1. So, Harris's standard can also be used to detect aCL directed only against phospholipid and not against the complex β 2GP1-cardiolipin. In addition, the use of Harris's standards seems to be better adapted to the detection of polyclonal antiphospholipid antibodies, than monoclonal human aCL used as internal controls.

The β 2GP1 present 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 ensure that this purified protein was not contaminated.

For every antibody determination, aCL and anti-β 2GP1 autoantibodies, normal levels were established from soddi of a large number of normal subjects (blood donors) as previously described. 7 In this study, 30 serum samples, provided by consenting healthy donors, were tested as controls.

Cut off values were determined as the mean and two standard deviations of the arbitrary units obtained by reference to positive and negative internal standards. For every serum, we defined the corrected optical density (OD) (that is, the mean OD obtained in three coated wells minus the OD corresponding to non-specific binding of each serum, obtained in three uncoated wells). The cut off values defined for anti-β 2GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β 2GP1 test were prepared to 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-β 2GP1 antibodies in normal sera. The percentage of positive normal serum samples was <3%. These differences between our results and those of Ambrozic et al are probably associated with a differing sensitivity 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 postoperative 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. 24 Indeed, in a community based, observational study of methotrexate use in 460 patients we found the...
perioperative period to be especially hazardous for patients with renal impairment and sepsis. Two subjects developed pancytopenia under these conditions, one of whom died.

Although all consecutive patients were included in the study by Grennan et al, it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made about the prevalence of this in the study group. It is important to note that this is a study of methotrexate use in elective surgery.

We suggest caution should be taken in patients with renal impairment (best assessed by creatinine clearance) and in the elderly with comorbid cardiovascular disease when approaching surgery. Sudden volume loss, bleeding, or dehydration will impair methotrexate excretion and increase the risk of bone marrow toxicity in this group. It may be prudent in those assessed as at high risk of this complication to stop methotrexate one week before the operation and restart treatment one or two weeks after the operation, depending on postoperative progress. This time period without methotrexate treatment will not 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 subjects with chronic renal failure and sepsis, and we would not disagree with this point. The risk of surgery is increased by any coincidental medical disease including renal failure and sepsis as well as chronic vascular disease. We noted this in our study.

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

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LETTERS

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

It is rare for coeliac disease to present only with symptoms of osteomalacia, without the classic symptoms of diarrhoea, steatorrhoea, and abdominal discomfort.5 6 A 22 year old woman presented with 18 months of a waddling gait, dyspnoea on exertion, and back pain. She had undergone a right hip arthroplasty after septic arthritis due to Pseudomonas aeruginosa. She had a 2 year history of chronic fatigue, and a further history of mild tiredness after eating gluten foods. She denied anaemia, gastrointestinal symptoms, or a family history of coeliac disease. Useful screening blood tests include determination of antigliadin and antiedomysial 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/DR7.5 6 Secondary hyperparathyroidism can develop in the case of bone turnover.5 6 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 6

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 antiedomysial 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/DR7.5 6 Secondary hyperparathyroidism can develop in the case of bone turnover.5 6 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 6

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References

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References
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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).\(^2\) Few studies have measured these levels in tissues, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of inflammatory responses. 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.\(^1\)

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.\(^3\) 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 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 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.

Results are given as mean (SD) and may be due to increased hepatic synthesis. Gastroenterology 1992;231:403–6.

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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Copper and zinc levels in plasma and PBMCs of patients with RA. Results are given as mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active RA</td>
</tr>
<tr>
<td>Plasma zinc (µg/l)(^*)</td>
<td>687 (467)</td>
</tr>
<tr>
<td>PBMC zinc (µg/10⁶ cells)(^†)</td>
<td>135.2 (28.6)</td>
</tr>
<tr>
<td>Plasma copper (µg/l)(^*)</td>
<td>1646 (357)</td>
</tr>
<tr>
<td>PBMC copper (µg/10⁶ cells)(^*)</td>
<td>58.0 (43.2)</td>
</tr>
</tbody>
</table>

PBMCs, peripheral blood mononuclear cells; there was no correlation between age, duration of disease, rheumatoid factor positivity, or any other single disorder 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).†Overall 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 overall a negative correlation between plasma and PBMC levels (p<0.05); †Overall, 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); †Overall, patients with RA had lower levels than controls (p<0.01) and those with active RA and those with inactive disease (p<0.01). 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 increases in people over 70 and increases with age. When a paraprotein is detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance. Owing to their immunochromeproperties, paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the so-called cold agglutinins. 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 nercrotising 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 his finger became necrotic. Angiography of his hand. In the following days the upper part of his right leg disappeared and on the left foot the necrosis began to demarcate to the end arterial vessels of her feet. Laboratory examination showed purpura skin lesions on the ear. A paraprotein was detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance. 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.

Patient B was a 60 year old man who was admitted to our hospital in January 2000 with Raynaud’s phenomenon of his ears, which consisted exclusively of the M component (IgG<sub>3</sub>). Further laboratory examination showed purpura skin lesions on the ear. A paraprotein was detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance. 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.

Patient C was a 78 year old woman who was admitted to our hospital in May 2000 with cyanosis in both feet, indicating possible arte- rial occlusion. During the following weeks both feet were cold and very painful. Angiography showed normal vessels, which strongly suggested vasculitis of the end arterial vessels of her feet. Laboratory examination showed purpura skin lesions on the ear. A paraprotein was detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance. 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.

References


Cryoglobulinaemic vasculitis as presenting manifestation of infective endocarditis

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

Case 1

In November 1994 a 63 year old woman presented with fever, purpura, paraesthesia, and pseudoaxial 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 of the feet and legs; mild ideomotor slowing down; shaky movements; and unsteady gait. An electro-physiological study recorded a moderate sensorimotor peripheral neuropathy, while ECG, chest x-ray examination, abdominal echography, and ecocardiography were normal. Cutaneous purpura biopsy disclosed a leukocycto–vasculitic vasculitis. Truncocerephal magnetic resonance imaging showed multiple, T2 weighted high signal intensity, punctiform lesions at the white matter consistent with brain vasculitis. Thus a central and peripheral neuropathy complicating CV was established, and prednisone (50 mg) combined with cyclophosphamide (100 mg) was given daily. However, the patient’s clinical status progressively worsened, and, finally, she died owing to cardiorespiratory failure four months after treatment. Necropsy disclosed coarse endocardial vegetations on the left side valves infected by Staphylococcus aureus.

Case 2

In January 1999 a 75 year old woman with no risk factors for infections presented with fever, purpura, and acropaesthesia. 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, acropaesthesia, and impairment of distal muscle strength. An electrophysiological study confirmed a sensorimotor peripheral neuropathy. Thus a higher steroid dose (50 mg/day) was given. A week later fever persisted and the patient complained of precordial pain and cardiac murmurs were found. A chest x-ray examination and transoesophageal echocardiography detected cardiomegaly and endocardial vegetations on the tricuspid valve; in addition, Staphylococcus aureus infection was shown by repeated blood cultures. Despite appropriate antibiotic treatment, the patient died one month later because of severe cardiorespiratory failure.

Discussion

Our two patients show some interesting peculiarities: the unusual presentation of IE...
as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the so-called "myocardial presentation" of IE symptoms together with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the fatal outcome. Previous reports (Medline) show that the association of IE with "asymmetric" cryoglobulinaemia is not uncommon; but only a few studies report IE clinically presenting as CV. This latter presentation can mean a diagnosis of another disease, moreover, steroid treatment can contribute to masking and worsening of the underlying infectious disorder. In the CV of our patients we can reasonably exclude the possibility that IE represented a complication of the CV. In over 300 of our patients with CV, bacterial manifestations have rarely been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in our two patients had quite unusual clinical and virological characteristics: absence of HCV or other hepatotropic viruses; the presence of particularly severe skin purpura; and the presence of neuropathy as important organ involvement. The peripheral neuropathy, in one case associated with central nervous system vasculitis, was the only prevalent organ manifestation seen in our patients. This is one of the most common clinical manifestations in patients with CV, but the aetiopathogenesis of which is still unclear. In a considerable number of patients with IE negative blood cultures have also been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in over 300 of our patients with CV unrelated to HCV infection and adequate treatment are essential. In conclusion, CV may represent the prevalent organ manifestation seen in patients with CV, as described elsewhere. The IIF staining pattern was as follows: nine (26%) pANCA, seven (20%) xANCA, and five (14%) cANCA. ANCA antibodies in Graves’ disease Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hyaluronidase, 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 xANCA when a distinct, homogeneous, peripheral accentuation was seen, as pANCA, as described elsewhere. The IIF staining pattern was as follows: nine (26%) pANCA, seven (20%) xANCA, and five (14%) cANCA. 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%) xANCA, and five (14%) cANCA. ELISA was positive in just one case (for MPO). 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 xANCA 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-Centre) as described elsewhere. The IIF staining pattern was as follows: nine (26%) pANCA, seven (20%) xANCA, and five (14%) cANCA. 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%) xANCA, and five (14%) cANCA. ANCA (IIF) were detected in 21 (60%) of the serum samples. The titre ranged from 1/40 to 1/2560. 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Lupus relapse after prostaglandin E, administration: activation of a cytokine cascade?

A variety of abnormalities in cytokine production occur in human and murine lupus, but their specific role in lupus pathogenesis is unknown. Recent in vitro studies emphasise the role of prostaglandins in the cytokine induction and modulation of the humoral immune response.1 We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E, (PGE,) administration, which to our knowledge has not been previously reported.

A 25-year-old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud’s phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy proving 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 prednisolone, 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 (Pharminagen, San Diego, CA), as previously described.1 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.1,11 A change in the proportion of Th2 cytokines might be associated with the polyclonal B cell activation seen in SLE.1 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.1 On the other hand, in some studies it has been suggested that PGE, alterations the Th1/Th2 balance of T cells to a dominant Th2 response.1 We suggest that the rise in IL4 production induced by 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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References


Table 1

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Basal PGE&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Basal PGE&lt;sub</td>
</tr>
<tr>
<td>Control</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Patient</td>
<td>1.2</td>
<td>1.1</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 osteoblastic activity, is inversely correlated with the extent of joint inflammation. Synovial and serum 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; age at diagnosis (11) years; disease duration (9) 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 radon treatment as prescribed by the patient's doctor. Patients were advised not to change their drug treatment. The ESR was determined according to Westergren, the result at one hour being taken to be low or normal.

The following laboratory values were used to test significance.

-Values at the first measurement were ESR 4–7 (mm/1st h), serum osteocalcin 26.1 (18.9, 32.7) ng/ml.
-Values at the second measurement were ESR 57 (mm/1st h), serum osteocalcin 25 (18, 31) ng/ml.

Results are given as median (25th, 75th).

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Table 1

<table>
<thead>
<tr>
<th>Immunological data of the patient</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lyphocyte count (×10^9/l)</strong></td>
<td>1.5</td>
<td>&gt;2</td>
</tr>
<tr>
<td><strong>IgG (g/l)</strong></td>
<td>23.3</td>
<td>(8-19.4)</td>
</tr>
<tr>
<td><strong>IgA (mg/l)</strong></td>
<td>6290</td>
<td>(620-3980)</td>
</tr>
<tr>
<td><strong>IgM (mg/l)</strong></td>
<td>531</td>
<td>(240-3920)</td>
</tr>
<tr>
<td><strong>CD3 (×10^9/l)</strong></td>
<td>1.2</td>
<td>0.7-4.2</td>
</tr>
<tr>
<td><strong>CD4 (×10^9/l)</strong></td>
<td>2.0</td>
<td>0.3-2.0</td>
</tr>
<tr>
<td><strong>CD8 (×10^9/l)</strong></td>
<td>1.0</td>
<td>0.3-1.8</td>
</tr>
<tr>
<td><strong>CD19 (×10^9/l)</strong></td>
<td>0.3</td>
<td>0.2-1.6</td>
</tr>
<tr>
<td><strong>CD3/CD16+CD56 (×10^9/l)</strong></td>
<td>0.2</td>
<td>0.1-0.9</td>
</tr>
</tbody>
</table>

References

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 immunologic cause and, possibly, an autoimmune process. 

Low CD4+ T lymphocyte counts are rare in patients, but conclusive evidence is lacking. 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 0.4x10^7/l, to determine the natural history of their infections and lymphopenopaenia. Two recent preliminary reports suggest that low CD4+ lymphopenia may cause dysgammaglobulinemia 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 disease manifestation had started three years before, when the patient suddenly presented with diplopia and painful periorbital and eyelid oedema. Limited abduction of the right eye was present. The treating ophthalmologist, after a thorough investigation that excluded brain tumours, orbital masses, and myasthenia gravis, prescribed naproxen (20 mg/kg/day) and systemic corticosteroid treatment (prednisone 1 mg/kg/day, tapered and withdrawn after 15 days); symptoms recovered completely in two weeks. A first magnetic resonance imaging (MRI) scan of the orbit had shown first degree exophthalmos 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 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 exophthalmos 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, anticyclic, antinuclear antithrombin 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 extraocular muscle 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 oculocardiac syndrome 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. Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, ScI, 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 extracul
Hodgkin’s lymphoma is rare. Systematic and vertebrae by low grade non-lymphoma. Sciatica or spinal lymphoma has 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 ocular myositis in the differential diagnosis.

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References

Sciatica or spinal lymphoma

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

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

He had a past history of epilepsy, which was controlled by phenytoin and phenobarbital. In 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypoplasia. Splenectomy was performed in 1994, his blood count returned to normal, and repeated full blood counts were stable. In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis but no infiltration. Treatment was started with 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 isotopic 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 unusual and normally resolve after immunosuppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

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

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was $4.89 \times 10^9/\text{L}$ with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal $<80$), and total IgE 769 IU/ml (normal $<100$), with 22% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed widespread eosinophilic bowel infiltration and vascular fibrinoid necrosis in the ileal wall were found. Bowel histology showed peritoneal cavity and two perforations in the 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, owing to right upper quadrant pain. 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 the Churg-Strauss syndrome. Medicine (Baltimore) 1999;78:26–27.

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.
Unusual complications in the Churg-Strauss syndrome

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