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 β glycoprotein I (β2GPI) dependence of the aCL was not defined, even though the authors focused on β2GPI independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines the antibodies detected by the classical aCL enzyme linked immunosorbent assay (ELISA).2—That is, both β2GPI dependent and β2GPI independent antibodies.

There were some potential methodological errors in determining β2GPI independent aCL. It was shown that antibodies against β2GPI (anti-β2GPI) from patients with the antiphospholipid syndrome (APS) have the ability to bind to β2GPI in complexes with cardiolipin only if the β2GPI concentration in solution is high enough. The threshold concentration of β2GPI was found to be just about 2 μg/ml, because no binding of anti-β2GPI was seen when serum samples were diluted 1:200 or more.3 As the physiological concentration of β2GPI in human serum is approximately 200 μg/ml, the threshold binding concentration is reached at a serum dilution of 1:100. In the presence of a relatively high concentration of endogenous β2GPI, the statement that antibodies detected by this method are exclusively β2GPI independent is unjustified, as the sera containing high titres of anti-β2GPI might have yielded positive results by the method described in the letter.

The definition of antibody units in the letter is not clear and using Harris’s standards for β2GPI independent aCL is not appropriate. With the use of Harris’s standards,2 the units should be abbreviated as GPl (for IgG) and MPL (for IgM) as previously defined.1 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, 1 β2GPI dependent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standards for β2GPI independent assays.

The interpretation of the aCL ELISA as a method to detect β2GPI dependent aCL may not be valid in all cases. It was shown that not all anti-β2GPI binding β2GPI adsorbed on polystyrene high binding plates also recognised β2GPI associated with cardiolipin. We reported this binding pattern for anti-β2GPI in children with atopic dermatitis,2 and the same was shown also for some patients with autoimmune diseases, including APS.2

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.3 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,4 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 described by calculating the mean + 2 SD of logarithms of absorbance values for NHS and the 95th centile value of 12 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.5 The β2GPI preparation did not contain any immunoglobulins. β2GPI independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for both β2GPI dependent aCL on the same plate by adding β2GPI in parallel duplicate wells. The final concentration of β2GPI was 10 μg/ml. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β2GPI. For the final determination of β2GPI dependent binding, the values obtained in wells without β2GPI were subtracted from the values measured in wells with added β2GPI. The patients’ histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the χ2 test where appropriate.

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

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

<table>
<thead>
<tr>
<th>No of positive samples:</th>
<th>Anti-β2GPI*</th>
<th>β2GPI dependent aCL†</th>
<th>β2GPI independent aCL‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>IgA</td>
</tr>
<tr>
<td>NHS (n=53*, n=32†)</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RA (n=53)</td>
<td>3</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>RA-RF (n=36)</td>
<td>6</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>RA - RF (n=17)</td>
<td>1</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; β, β2GPI, β glycoprotein I; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.
any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2GPI and β2GPI dependent aCL of IgA isotype. Interestingly, 5/11 RA sera which showed binding to β2GPI adsorbed on a high binding plate did not recognise β2GPI associated with cardiolipin, as already reported. In contrast, 3/9 RA sera binding to β2GPI complexed with cardiolipin did not recognise β2GPI adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2GPI in RA, which may differ in fine specificity between anti-β2GPI in APS.

The sera from our patients with RA exhibited an even higher frequency of β2GPI independent aCL than that reported in the literature. As expected from reported data, the presence of β2GPI independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GPI (10 μg/ml) lowered the binding of β2GPI independent aCL by about 50%, most probably owing to the competition between β2GPI independent aCL and β2GPI for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2GPI and β2GPI dependent aCL which might be associated with the signs of APS. The importance of distinguishing β2GPI independent aCL has not been fully clarified. It seems that the presence of independent aCL do not confer an increased risk for RA.

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References

Authors' reply
In response to the comments of Ambrozic et al we would like to give additional information to the data published earlier in the Annals.7 The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera by the presence of high binding plates. This phenomenon is already reported.

In contrast, 3/9 RA sera showed binding with β2GPI complexed with cardiolipin did not recognise β2GPI adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2GPI in RA, which may differ in fine specificity between anti-β2GPI in APS.

The sera from our patients with RA exhibited an even higher frequency of β2GPI independent aCL than that reported in the letter. As expected from reported data, the presence of β2GPI independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GPI (10 μg/ml) lowered the binding of β2GPI independent aCL by about 50%, most probably owing to the competition between β2GPI independent aCL and β2GPI for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2GPI and β2GPI dependent aCL which might be associated with the signs of APS. The importance of distinguishing β2GPI independent aCL has not been fully clarified. It seems that the presence of independent aCL do not confer an increased risk for RA.

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

Although all consecutive patients were included in the study by Brennan 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 case series, and the results should be viewed with caution.

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-

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.1 A 22 year old woman presented with 18 months of a waddling gait, disturbed nutrition, IP and back x rays were normal. She experienced bone pain when being hugged, when laughing, or coughing, and had difficulty standing up from a low chair and holding her arms up to blow-dry her hair. She had extreme tiredness and thought she might have lost some weight, but there were no gastrointestinal symptoms. On examination, she was pale and had difficulty squatting and holding her arms above her head.

Investigations showed a mild anaemia secondary to β thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphatase of 1375 U/l (normal 30–120 U/l), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.0 mmol/l (0.8–1.4 mmol/l), 25-hydroxy vitamin D <5 nmol/l (15–110 nmol/l), and raised parathormone 53.1 pmol/l (1.0–6.5 pmol/l). Investigations were carried out for a malabsorption syndrome. Antigliadin, antitymoma, and antiglutamin 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. Osteopenosis was demonstrated by dual emission x ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm² (2.65 SD below the young adult female mean) and the neck of the femur 0.633 g/cm² (2.9 SD below the mean).

Treatment involved a gluten free diet, ergocalciferol 3000 IU daily, calcium carbonate 600 mg twice a day, slow release ferrous sulphate 350 mg daily, and folinic 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 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.2 Most patients were middle aged, and responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates.3 A recent case finding study of coeliac disease showed that many patients in fact present with non-gastrointestinal symptoms, of which anaemia is the most common.4

Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area, secondary hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed dietary fatty acids to form insoluble calcium soaps.5

Secondary hyperparathyroidism can develop if this is not diagnosed. 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.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 antitymoma antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.7 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/DR7.8

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.4 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.9 Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.6

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

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

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) [1,2] and osteoporosis [3]. Few studies have measured these levels in tissues, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of immunological aberrations [4]. 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 [5].

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 [6]. 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 lyzed PBMC samples were read on an atomic absorption spectrophotometer (Perkin Elmer, Norwalk, CT) at a wavelength of 213.8 nm for Zn and 324.7 nm for Cu. The atomic absorption spectrophotometer was calibrated with reference standards obtained from Sigma Chemicals Company (St Louis, MA).

Thirty nine patients (31 women) with RA had a mean (SD) age of 36.2 (8.3) years (range 18–52) and mean disease duration of 35.8 (36.6) months (range 6–168). 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 in patients with active RA [7]. Additional findings herein 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 must be considered. The number of patients receiving non-steroidal anti-inflammatory drugs 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 patients to those seen in controls. Hence, further studies need to be carried out on paired samples in a cohort of patients, once the disease is active and again when it becomes inactive.

Phenomenon, arthralgia-arthritis, and skin lesions

The relevance of monoclonal gammopathy in relation to rheumatic disorders has recently been reviewed [8]. Monoclonal gammopathy or...

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### Table 1 Copper and zinc levels in plasma and PBMCs of patients with RA.

<table>
<thead>
<tr>
<th></th>
<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma zinc (µg/l)*</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>Plasma 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>98.4 (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>Plasma Cu (µg/10^6 cells)</td>
<td>58.0 (43.2)</td>
<td>74.9 (37.2)</td>
<td>84.0 (33.2)</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). Overall levels were significantly higher in patients than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). There was overall a negative correlation between plasma and PBMC zinc levels (p<0.05); 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<0.05) and those with active RA as compared with those with inactive disease (p<0.01). There was a negative correlation between plasma and PBMC copper levels (p<0.05).

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References


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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 [8]. Monoclonal gammopathy or...
paraproteins can be detected in healthy adults and in different disease entities like amyloidosis, malignant proliferative disorders,1 associated with hepatitis C infections,1 and rheumatic diseases.2 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 existence 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 suggested 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 both hands became necrotic. Angiography of the arteries showed normal vessels. Immune electrophoresis showed the presence of 8 g/l of an M component (IgG). An assay for the detection of cryoglobulinaemia was positive. Laboratory examinations showed no abnormalities. Virus serology showed that the cryoglobulins were formed by the monoclonal gammopathy of undetermined significance (IgGa). Other laboratory examinations showed no abnormalities. Viral serology showed only the presence of a cryoglobulinaemia. She was treated with chlorambucil (8 mg/day) and prednisone (60 mg/day), which improved the necrosis of her legs. The necrosis of her right leg disappeared and on the left foot the necrosis began to demarcate to the upper part of her foot. While waiting for the complete demarcation so that an amputation could be planned, she developed a sepsis and died.

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

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

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References


Cryptoglobulinaemic vasculitis as presenting manifestation of infective endocarditis

Seromunomological alterations, including antibodies and/or cryoglobulins, are common in patients with infective endocarditis (IE), however, specific autoimmune disorders, such as cryoglobulinaemic vasculitis (CV) associated with IE have seldom been described. CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and complement; 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, paraesthesias, and pseudoaxotic gait. Her past clinical history was unremarkable except for a prosthetic implant of the left hip four years previously. Table 1 shows the main clinicianserological features. Repeated blood cultures were negative. Neurological examination showed abnormal tactile sensation of the feet and legs; mild idemotor slowing down; shaky movements; and unsteady gait. An electrophysiological study recorded a moderate sensorimotor peripheral neuropathy, while ECG, chest x ray examination, abdominal echography, and echocardiography were normal. Cutaneous purpura biopsy disclosed a leukocytoclastic vasculitis. Truncocerehal magnetic resonance imaging showed a 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 cardiopulmonary failure following a month of treatment. Necropsy disclosed coarse endocardial vegetations on the left sided valves infected by Kugella.

Case 2

In January 1999 a 77 year old woman with no risk factors for infections presented with fever, purpura, and acroparaesthesias. Table 1 shows the main clinical and laboratory features suggestive of CV. Prednisone (25 mg/day) was started, with a rapid clinical improvement. One month later, she had an exacerbation of purpura, paraesthesias, 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 treated valves; in addition, Staphylococcus aureus infection was shown by repeated blood cultures. Despite appropriate antibiotic treatment, the patient died one month later because of severe refractory heart failure.

Discussion

Our two patients show some interesting peculiarities: the unusual presentation of IE

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

In our patients we can reasonably exclude the possibility that IE represented a complication of the CV. In over 300 of our patients with CV, bacterial manifestations have rarely been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in our two patients had quite unusual clinical and virological characteristics: absence of HCV or other hepatotropic viruses; the presence of particularly severe skin purpura; and the presence of neuropathy as important organ involvement. The linked immune, 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, the aetiotopathogenesis of which is still unclear. In a considerable number of patients with IE negative blood cultures have also been recorded. Often when Gram negative bacteria are involved.

In patient 1, the lack of timely recognition of Kingella by repeated blood cultures was probably due to different reasons, including slow growing of the agent, low microbial charge in the blood samples, and/or inappropriate use of growth media. However, the negative cultures together with clinical symptoms suggestive for CV, in the absence of relevant features at trans thoracic echocardiography at the onset, were sufficient reasonably to exclude a suspicion of IE presenting as CV. In conclusion, CV may represent the presenting manifestation of IE, a life threatening infectious disorder.

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

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

*HBsAg, anti-HBs, anti-HBcIgM, anti-HBc, anti-HCV by ELISA and RIBA; anti-EBV IgM; anti-HIV.

ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmatic antibodies (ANCA) positivity—namely, hydralazine, penicillamine, allopurinol, and propylthiouracil. Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis, other antimydrugs, 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 cytoplasmatic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed and as xANCA when a distinct, homogeneous, non-granular cytoplasmatic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere. Hospital Universitari Germans Trias i Pujol is a 533 bed hospital situated on the outskirts of Barcelona. It is a referral hospital serving a population of 700 000 inhabitants. The immunology laboratory is a reference centre.

ANCA (IF) were detected in 21 (60%) of the serum samples. The titre ranged from 1/40 to 1/2560. The immunofluorescence staining pattern was as follows: nine (26%) pANCA, seven (20%) xANCA, and five (14%) cANCA. ELISA was positive in just one case (for MPO)—in the patient with an IF titre of 1/2560.

Our results are very similar to those of Aeflitta et al, who reported ANCA positivity by IF in 6/21 (29%) patients with Graves’ disease. The IF staining pattern was cANCA in five cases and xANCA in one case. Anti-MPO autoantibodies were detected only in one (5%) of the patients. In our study ANCA were detected in 21 (60%) serum samples. The IF staining patterns were more heterogeneous, but the ELISA results were similar.
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. We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E (PGE), administration, which to our knowledge has not been previously reported.

A 25 year old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud's phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy proven diffuse proliferative lupus glomerulonephritis (WHO class IV). A physical examination showed only painful, violaceous, and atrophic x-ray films were normal and laboratory investigations showed an 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 after 45 minutes without adverse events, 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 (Pharminen, San Diego, CA), as previously described. The test performed eight months after 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 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.
osteoalac: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation. Synovial and serum osteocalcin correlate positively. In ankylosing spondylitis (AS) the serum concentration of osteocalcin, which has been reported to be low1–2 or normal.3 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.4 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.5

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age 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, hydrotherapy, electrotherapy, underwater exercises, and oral 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 time being used for calculation. Serum was frozen at −18°C until further analysis. Osteocalcin was measured in one batch with a commercially available test kit (IRMA, Biocis, Vienna; manufactured in one batch with a commercially available test kit). Osteocalcin was measured in one batch with a commercially available test kit (IRMA, Biocis, Vienna; manufactured in one batch with a commercially available test kit). The Mann-Whitney rank sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 18 (8, 28) mm/1st h, serum osteocalcin 25 (20.5, 52.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/1st h, osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR and osteocalcin in 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, 5.7) ng/ml showed a significant correlation (r = 0.28, p < 0.01).

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

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CD4+ lymphopenia may cause dysgamma-globulinaemia and autoimmune syndromes such as Takayasu arteritis.

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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 determined the natural history of their infections and lymphocyte-penia, referred the patient to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia.

Methods

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 determined the natural history of their infections and lymphocyte-penia, referred the patient to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia.

Results

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 determined the natural history of their infections and lymphocyte-penia, referred the patient to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia.

Conclusions

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 determined the natural history of their infections and lymphocyte-penia, referred the patient to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia.

References


Figure 1

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

Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-aorta antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.7

Low CD4+ T lymphocyte counts are rare in the absence of immunodeficiency; most commonly infection with HIV.8 In our patient, major histocompatibility complex II deficiency was excluded by the expression of HLA-DR on peripheral blood lymphocytes. Serological testing for HIV infection was negative and, additionally, the patient had no risk factor for transmission of HIV infection or recent immunosuppressive treatment.

All patients with idiopathic CD4+ T lymphocytopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4 x 109/l to determine the natural history of their infections and lymphocytopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking.8

The investigations of cases of idiopathic depletion of CD4+ T lymphocytes indicate that they probably represent various disorders, and that in some cases, low CD4+ T lymphocyte counts may reflect transient responses to infections or other conditions such as autoimmune disorders.9 In patients with aorta arteritis, immunological investigations have shown a decrease in the titre of complement and phagocytic activity of neutrophil granulocytes, deep depression of T cell immunity, and hypergamma-globulinaemia.9 Wiskott-Aldrich and Takayasu arteritis have been reported previously.1 It is rare for patients to have both disorders and with this case report, we draw attention to this association. This case report suggests that low

Figure 1

Orbital MRI (T1 weighted image with contrast) that shows increased signal and size of the right rectus lateralis muscle.
Hodgkin’s lymphoma is rare. Systematic and vertebrae by low grade non-
Sciatica or spinal lymphoma

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

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References

Sciatica or spinal lymphoma

The involvement of the central nervous system and vertebrae by low grade non-Hodgkin’s lymphoma is rare.1 In a previous “lesson of the month”2 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 ophthalmoscopy, the erythrocyte sedimentation rate was 4 mm/1 h, a myeloma screen was negative, and prostatic specific antigen was normal.

Figure 1 Sagittal MR scan of the spine showing vertebral infiltration, being most intense in L2 and L5, which is biconcave (arrows).

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 unusual3 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 1×10^9/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed calcaceous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right aneckotomy 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 <10), 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 granular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinuous 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 ovarian 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, pending a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right aneckotomy were performed.

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

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.
22nd European Workshop for Rheumatology Research
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Fax: 216 445 7569
Email: borkd@ccf.org
Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

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Website: www.eular.org

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Website: www.userpages.fu-berlin.de/~zoubbere
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