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. 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),—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, the units should be abbreviated as GPL, (for IgG) and MPL, (for IgM) as previously defined. However, Harris’s standards were used for design in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominately, β2GPI dependent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standard for β2GPI independent assays.

The interpretation of all 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 recognise β2GPI associated with cardiolipin. We reported this binding pattern for anti-β2GPI in children with atopic dermatitis, and the same was shown also for some patients with autoimmune diseases, including APS.

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. In addition, the authors did not report the proportion of NHS positive for each assay and the values of positive samples compared with patients with RA. Instead, they just referred to one study, which is only one of the several published estimations of aPL in healthy subjects.

We would like to support our criticism by adding some data about aPL in our patients with RA. We randomly selected 53 serum samples from patients fulfilling the ARA criteria for RA and 53 NHS as negative controls. The samples were tested for anti-β2GPI, β2GPI dependent aCL, and β2GPI independent aCL. The assays were calibrated with β2GPI dependent 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 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. The β2GPI preparation did not contain any immunoglobulin. 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 Chi 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...
any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2-GP1 and anti-β2-GP1 dependent aCL of IgA isotype. Interestingly, 7/11 RA sera which showed binding to anti-β2-GP1 adsorbed on a high binding plate did not recognise β2-GP1 associated with cardiolipin, as already reported. In contrast, 3/9 RA sera binding β2-GP1 complexed with cardiolipin did not recognise β2-GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2-GP1 in RA, which may differ in fine specificity to anti-β2-GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β2-GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β2-GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2-GP1 (10 μg/ml) lowered the binding of β2-GP1 independent aCL by about 50%, most probably owing to the competition between β2-GP1 independent aCL and β2-GP1 for the same binding sites on cardiolipin. In conclusion, patients with RA may have anti-β2-GP1 and β2-GP1 dependent aCL which might be associated with the signs of APS. The importance of distinguishing β2-GP1 independent aCL has not been fully clarified. It seems that the presence of 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 offer some information to the data published earlier in the Annals.2

The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera by specific ELISA. The concentration of aCL on β2-glycoprotein 1 (β2-GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2-GP1 in blocking buffer (containing fetal calf sera or bovine sera). In our standard ELISA 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 β2-GP1. This method justified the terminology of β2-GP1 independent aCL for sera containing aCL without anti-β2-GP1 antibodies. The absence of anti-β2-GP1 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 β2-GP1 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 β2-GP1 in the assays used for the detection of β2-GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2-GP1) did not react with β2-GP1 in the other ELISA test specifically designed to detect anti-β2-GP1 autoantibodies, and therefore which could detect hypothetically high titres of anti-β2-GP1 antibodies contained in these sera.

Harris’s standards were used after calibration of our positive control sera from patients with proven antiphospholipid syndrome (APS), which were used in the positive controls for every microtitre plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera.2 The antiphospholipid antibodies, including aCL, are directed against several anti-gens targets. Among them, some epitopes are located on the cardiolipin alone. These data were described by Harris when aCL were first characterised in systemic lupus 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.1 These reagents were constituted by lipids alone without any other cofactor such as β2-GP1. So, Harris’s standard can also be used to detect aCL directed only against phospholipid and not against the complex β2-GP1-cardiolipin. In addition, the use of Harris’s standards seems to be better adapted to the detection of polyclonal anti-phospholipid antibodies, than monoclonal human aCL used as internal controls.

The β2-GP1 used in our assay was provided by Stago laboratories (Asnières, France) and was purified from human sera. We used sodium dodecyl sulphate-polyacrylamide gel electrophoresis and immunoblotting to ensure that this purified protein was not contaminated.

For every antibody determination, aCL and anti-β2-GP1 autoantibodies, normal levels were established from sera of a large number of normal subjects (blood donors) as previously described.3 In this study, 50 serum samples, provided by consenting healthy donors, were tested as controls.

Cut off values were determined as the mean and two standard deviations of the arbitrary units obtained by reference to positive and negative internal standards. For every serum, we defined the corrected optical density (OD) (that is, the mean OD obtained in three coated wells minus the OD corresponding to non-specific binding of each serum, obtained in three uncoated wells). The cut off values defined for anti-β2-GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2-GP1 test with the addition of positive controls from patients with APS and were used according to previous studies.4

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2-GP1 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.1 Previous investigators have despaired of answering this question definitively owing to the difficulty in recruiting subjects.2 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 with significant caution. The elderly and those with renal impairment are at increased risk of methotrexate-related pancytopenia.3,4 Indeed, in a community based, observational study of methotrexate use in 460 patients we found the
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.\(^6\)\(^,\)\(^7\)

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

Investigations showed a mild anaemia secondary to \(\beta\) thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphate of 1375 U/l (normal 30–120 U/l), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.0 mmol/l (0.81–1.4 mmol/l), 25-hydroxy vitamin D <5 nmol/l (15–110 nmol/l), and raised parathyroid hormone 53.1 pmol/l (1.0–6.5 pmol/l).

Investigations were carried out for a malabsorption syndrome. Antigliadin, antienthymosial, and antiglutaminase antibodies were strongly positive, and a small bowel biopsy showed almost total villous atrophy, confirming the diagnosis of coeliac disease.

A bone scan demonstrated increased activity throughout the skeleton, consistent with secondary hyperparathyroidism. Osteoporosis was demonstrated by dual emission \(x\) ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm\(^2\) (2.65 SD below the young adult female mean) and the neck of the femur 0.635 g/cm\(^2\) (2.9 SD below the mean).

Treatment involved a gluten free diet, ergocalciferol 3000 IU daily, calcium carbonate 600 mg twice a day, slow release ferrous sulphate 350 mg daily, and folic acid 5 mg daily.

Within two months her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphate reduced to 374 U/l. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm\(^2\) (mean level for young adult women), and the neck of the femur by 39% to 0.878 g/cm\(^2\) (0.8 SD below the mean). She had also gained more than 7 kg in weight, and repeat gastroscopy and duodenal biopsy were normal.

Osteomalacia is now an uncommon disease, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965,\(^1\) there have been several more case reports of coeliac disease presenting with bone pain, proximal myopathy, radiographic findings of pseudoarthrosis 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.\(^6\) 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.\(^3\)

Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area, secondary hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.\(^4\)

Secondary hyperparathyroidism can develop, if it did in this case, causing increased bone turnover. Low bone mineral density is probably due to a combination of hypocalcaemia, impaired bone mineralisation, and reduced exercise because of skeletal pain and proximal weakness.\(^5\)

Early diagnosis of coeliac disease is important because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determination of antigliadin and antienthymosial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.\(^6\)\(^,\)\(^7\) 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.\(^7\)

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.\(^2\)\(^,\)\(^8\) The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.\(^4\) Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.\(^4\)

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

Patients attending the rheumatology clinic at our institute and satisfying the American Rheumatism Association criteria for the classification of rheumatoid arthritis (RA) were studied. 2,3 Few studies have measured these levels in tissues, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of events. 4–6 Plasma and PBMC Cu levels may merely be a reflection of an acute phase response, and the PBMC levels of Zn.

Plasma and PBMCs, peripheral blood mononuclear cells; there was no correlation between age or duration of disease and plasma or PBMC levels of Zn and Cu.

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

<table>
<thead>
<tr>
<th></th>
<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma zinc (µg/l)*</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>PBMC zinc (µg/10^9 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>PBMC copper (µg/10^9 cells)§</td>
<td>50.8 (43.2)</td>
<td>86.4 (33.2)</td>
<td>74.3 (38.2)</td>
<td>104.2 (8.5)</td>
</tr>
</tbody>
</table>

PBMCs, peripheral blood mononuclear cells; there was no correlation between age, duration of disease, rheumatoid factor positivity, or any 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). Toverall levels were significantly higher than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). There was an overall negative correlation between plasma and PBMC Zn levels (p=0.05); toverall, 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); toverall, patients with RA had lower levels than controls (p>0.05) and those with active RA had lower levels than those with inactive disease (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 gammapathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gammapathy or 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 Zn and Cu as controls. If the diet of patients with active RA were deficient in Zn (as shown by plasma levels) it would be unlikely to contain an excess of Cu and vice versa for PBMC levels. The more plausible explanation would be that this represents a redistribution of trace elements between plasma and PBMCs, and a control of inflammation would lead to an increase in the concentrations of Zn and Cu.

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paraproteins in adults is about 1%.

His finger became necrotic. Angiography of his hand. In the following days the upper part of the upper part of the third finger of his left patient A was a 69 year old man who, in May case reports and in different disease entities like amyloidosis, rheumatoid arthritis of the small joints and severe arthritis. Patient C was a 78 year old woman who was admitted to our hospital in May 2000 with cyanosis in both feet, indicating possible arterial occlusion. Both legs were cold and very painful. Angiography showed normal vessels, which strongly suggested vascular problems of the anterior tibial arteries of her feet. Laboratory examination showed a paraprotein (8 g/l) in the serum. 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 cryoprecipitated cryoglobulin was reduced, the disease symptoms in our patients improved. These cases suggest that a paraprotein found in patients with a rheumatoid syndrome is not only indicative of a developing malignancy or other disease but may also be interpreted as a causative agent. We conclude that paraproteins seen in rheumatic syndromes have a role in the pathogenesis and should be treated when serious sympoms are present. J G den Hollander Department of Internal Medicine, Zuiderzakenhuis, Rotterdam, Amsterdam

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References


Cryoglobulinaemic vasculitis as presenting manifestation of infective endocarditis

Seroimmunological alterations, including antibodies and/or cryoglobulins, are common in infective endocarditis (IE), a systemic rheumatic disease, and in 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, 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 clinicocerological features. Repeated blood cultures were negative. Neurological examination showed abnormal temporal tactile sensation in the face and legs; mild idiomotor 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 echocardiography were normal. Cutaneous purpura biopsy disclosed a leucocytoclastic vasculitis. Truimeocephalic magnetic resonance imaging showed 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. After 6 months of treatment, necropsy disclosed coarse endocardial vegetations on the left sided valves infected by Kragella.

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, 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 transeosophageal echocardiography detected cardiomegaly and endocarditis; vegetations on the tricuspid valve; and 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 neurological symptoms associated with CV were present 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,12,13 but only a few studies report IE clinically presenting as CV.14 This latter presentation can mean a misdiagnosis; moreover, steroid treatment can contribute to masking and worsening of the underlying infectious disorder.4

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 viruses15; the presence of particularly severe skin purpura; and the presence of neurophyathy 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,16,17 the aetiopathogenesis of which is still unclear. In a considerable number of patients with IE negative blood cultures have also been reported,18 often when Gram negative bacteria are involved.19

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 transesophageal 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 condition for which a timely correct diagnosis and adequate treatment are essential. In patients with CV unrelated to HCV infection and with fever unresponsive to steroids it is strongly recommended that other less common, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinicoclinimicrobiological evaluation, including transesophageal echocardiography.20

References


ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hydralazine, penicillamine, allopurinol, and propylthiouracil.21

Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis,22 other antithyroid drugs, such as carbimazole and thiamazole, have been linked.23 Furthermore, ANCA positivity has been described in the course of Graves’ disease without vasculitis.24

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 immuno-fluorescence (IF) on ethanol fixed granulocytes, as described elsewhere.25 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 using the commercially available enzyme linked immunoassay (ELISA; Organex) as described elsewhere.25 Hospital Universitari Germans Trias i Pujol is a 533 bed hospital situated on the outskirts of Barcel- lona. It is a referral hospital serving a population of 700,000 inhabitants. The immunology laboratory is a reference centre.

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

Our results are very similar to those of Afi- trra et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with Graves’ disease.26 The IIF staining pattern was cANCA in five cases and XANCA in one case. Anti-MPO auto- antibodies were detected only in one (5%) of the patients. In our study ANCA were detected in 21 (60%) serum samples. The IIF staining patterns were more heterogeneous, but the ELISA results were similar.

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

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
</tr>
<tr>
<td>Disease duration (weeks)</td>
<td>7</td>
</tr>
<tr>
<td>Purpura</td>
<td>Haemorrhagic papulonodular</td>
</tr>
<tr>
<td>Weakness</td>
<td>Severe</td>
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<tr>
<td>Arthritis</td>
<td>Recurrent</td>
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<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/1 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 × 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>GL (normal 17–34 mg/dl)</td>
<td>19.5</td>
</tr>
<tr>
<td>CRP (normal &lt;0.2 IU/ml)</td>
<td>&lt;60</td>
</tr>
<tr>
<td>C3 (normal 300–1200 mg/dl)</td>
<td>930</td>
</tr>
<tr>
<td>C4 (normal 200–550 mg/dl)</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Cryocrit, % (cryo-type)</td>
<td>0.5 (IgG-IgM)</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.
Human MPO and human thyroid peroxidase (TPO) share global similarities which indicate that MPO and TPO are members of the same gene family. Therefore, it seems conceivable that MPO autoantibodies may cross react with TPO. Findings suggesting such a relationship were reported by Haapala et al. who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and the last patients who were responsible for the ANCA positivity.

ANCA positivity in Graves' disease may be attributable to either antithyroid drugs (thi- mazole or propylthiouracil) or to the disease itself.

Acknowledgment

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

References


Lupus relapse after prostaglandin E, administration: activation of a cytokine cascade?

A variety of abnormalities in cytokine production occur in human and murine lupus, but their specific role in lupus pathogenesis is unknown. Recent in vitro studies emphasise the role of prostaglandins in the cytokine induction and modulation of the humoral immune response.11 We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E (PGE), administration, which to our knowledge has not been previously reported.

A 25 year old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud's phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy proven diffuse proliferative lupus glomerulonephritis, (WHO class IV). A physical examination showed only painful, violaceous, and atrophic finger pads with no signs of systemic inflammatory disorder. The chest x ray films were normal and laboratory investigations showed antinuclear antibodies (ANA; titre 1/160) and hypercomplementaemia (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 azathioprine, 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 stimulation was studied. Intracellular expression of cytokines in the patient's T lymphocytes after specific PGE stimulation was studied.

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.12 A change in the proportion of Th2 cytokines might be associated with the polyclonal B cell activation seen in SLE.13 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.14 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.15 We suggest that the rise in IL4 production induced by the PGE, as shown in vitro, in this patient, may be a marker of dysregulation of the Th1/Th2 profile and might have been the cause of her lupus relapse.

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References


Table 1

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE</td>
<td>Basal PGE</td>
<td>Basal PGE</td>
</tr>
<tr>
<td>Patient</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Control</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

IL, interleukin; INFγ, interferon γ.

Whole blood was incubated with or without PGE, 10 ng/ml, for six hours in the presence of Brefeldin A. Cells were stained with FITC-anti-CD3, PE-anti-IL4, and biotin anti-IL2 antibodies and then stained with anti-IL2 and anti-IL4 conjugates as previously described.16 The test performed eight months after the PGE treatment showed a dramatic rise in interleukin 4 (IL4) production (table 1).

Intracellular cytokine production after PGE stimulation in the patient and in an asymptomatic lupus patient who served as a control. Results are shown as the percentage of T lymphocytes with cytokine synthesis.
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation.1 Synovial and serum osteocalcin correlate positively.2 In ankylosing spondylitis (AS) the serum concentration was within the normal range in 75th centile). The Mann-Whitney rank sum test showed no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein.3

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 dominant Th2-like response on liver T cells in patients with experimental systemic lupus erythematosus. Nishimura H, Washizu J, Naiki Y, et al. Evidence of impaired cartilage/bone turnover in patients with active ankylosing spondylitis. Ann Rheum Dis 1995;54:233–41

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age 43 (11) years; disease duration 14 (8) years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, homeopathy, electrotherapy, underwater exercises, and radion treatment as prescribed by the patient's doctor. Patients were advised not to change their drug treatment. The ESR was determined according to Westergren, the result at one hour being 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; normal range according to the manufacturer 7.5–31.5 ng/ml in men, 3.7–31.7 ng/ml in women). Results are given as median (25th, 75th centile). The Mann-Whitney rank sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 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 at the first examination did not correlate significantly (r=0.07; p=0.5).

The changes in ESR (1 (−4, 6) mm/1st h) and in osteocalcin (2.3 (−2.6, 3.5) 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.
Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-aorta antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.7

Low CD4+ T lymphocyte counts are rare in the absence of immunodeficiency, most commonly infection with HIV. In our patient, major histocompatibility complex class II deficiency was excluded by the expression of HLA-DR on peripheral blood lymphocytes. Serological testing for HIV infection was negative and, additionally, the patient had no risk factor for transmission of HIV infection or recent immunosuppressive treatment. All patients with idiopathic CD4+ T lymphopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4x10^7/l, to determine the natural history of their infections and lymphocyteopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients to have both disorders and with this recent immunosuppressive treatment. Prednisone 2 mg/kg/day were administered (prednisone 1 mg/kg/day, tapered and withdrawn after 15 days); symptoms recovered and recurrence of orbital pain and diplopia subsided over a period of two months. After a short period of wellbeing, the disease flared up again, and recurrence of orbital pain and diplopia was observed when steroids were reduced to 0.5 mg/kg/day. The boy was then admitted to our unit. He appeared well, with no constitutional symptoms. Ocular examination showed mild right exophthalmus and limited motion of both eyes.

Laboratory tests including muscle enzymes (alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, aldolase) values, complement levels, and thyroid function were all within the normal range. Serological tests were negative for viral and bacterial infections, and antibodies against Borrelia burgdorferi were absent. Autoantibodies (antinuclear antibodies, anti-dsDNA, antiphospholipid, antinuclear antibodies, anticytoplasmic 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. Electromyography and two dimensional echocardiography excluded a concomitant myocardiitis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (Scl), Crohn's disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extraocular part 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 ocular disorder has been seen so far, and prednisone has been progressively reduced to the current dose of 5 mg/day.

The group of idiopathic inflammatory myopathies encompasses a variety of common and uncommon syndromes. The uncommon variants of myositis include orbital myositis, a condition that is rare in adults and even rarer in children.8 Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, Scl, giant cell myocarditis, and Crohn's disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease, ocular myopathies, such as mitochondrial disorders and ocular dystrophies; and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinuses thrombosis are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extracocular
muscles. MRI shows muscle oedema of the affected muscle(s), and is useful for monitoring disease activity. Non-steroidal anti-inflammatory drugs are recommended as first line treatment, but systemic steroids are required in most cases. When steroids fail to control muscle inflammation, methotrexate and cyclosporin have been used with success.1 In our patient, cyclosporin was successful as a steroid sparing agent, because a rapid recurrence of symptoms had always occurred in the past when the corticosteroid dose was reduced, and at present, after six months of cyclosporin treatment, the boy is still asymptomatic and receiving a low dose of steroids.

Despite the rarity of this disorder, our case suggests that diplopia in a child requires rapid and extensive investigation that must include isolated oculomotor palsies 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 lymphadenopathy. He had restricted movement with tenderness of lower lumbar spinal processes. Straight leg raising test was restricted to 45° bilaterally, and produced a positive Babinski sign. A lumbosacral spine x ray examination showed collapse of T7 and T8, with evidence of osteoporosis. The wedging of T4, with evidence of osteoporosis (fig 1).

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

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.

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 unusual1 and normally resolve after immuno-suppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

A 64 year old woman with a 13 year history of urticaria, recurrent rhinitis, and asthma was admitted for abdominal pain. An increasing peripheral eosinophilia rising from 1% to 22% in the past five years was detected. Two years before hospital admission an extensive urticaria entering remission developed. An abdominal ultrasonography performed during an asthmatic exacerbation when she had no abdominal pain disclosed a thick-walled gall bladder with no echogenic contents. An excised nasal polyp showed polypoid hyperplasia with many eosinophils.

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Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 1.05×10⁹/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 aneurectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.89×10⁹/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), 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 hyalin and hyalinelgranular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 55 g/l, a leucocyte count of 1.05×10⁹/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.1

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, with initial clinical improvement. However, the abdominal pain recurred and the patient underwent a second laparotomy after three weeks of treatment. Peripheral blood leucocytes were 18.1×10⁹/l with 1% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to 435 IU/ml. Purulent fluid in the peritoneal cavity and two perforations in the ileal wall were found. Bowel histology showed wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophil infiltrates. Granulomas were not found. E coli grew from the peritoneal fluid. Intravenous metronidazole and gentamicin were started. Four days later a new perforation was suspected and a third laparotomy was done, showing a perforated necrotic small bowel plaque. A broad bowel resection was performed but the patient’s evolution was complicated with high fever, ileus, and vomiting, and she died 48 hours later. A necropsy was not allowed.

Abdominal pain is reported in up to 25–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described, the last of these being responsible for up to 10% of the CSS deaths.1 Acalculous cholecystitis, although very rare, may be the first and sometimes the unique manifestation of the CSS.1,6 Its evolution is usually torpid, and sometimes only diagnosed at necropsy. Abdominal ultrasonography should be included in the routine screening of patients with CSS.

The right oophoritis was due to vasculitis, with an eosinophilic infiltrate suggestive of CSS (fig 1). As far as we know, this is the first reported case of CSS with confirmed oварium involvement.

The ascitic fluid, rich in eosinophils, the eosinophilic infiltration of major omentum samples and the clinical evolution suggest that the peritoneal involvement was due to the CSS, an extremely rare complication of this disease. Eosinophilic peritonitis was suggested by Lanham owing to serosal involvement in the CSS,5 but has only been confirmed in one case so far.1

The poor response to steroids and cyclophosphamide is striking. Despite the reduction of the peripheral eosinophilia and ESR there was widespread eosinophilic bowel infiltration and vascular fibrinoid necrosis in the laparotomy samples. The evolution of the disease in our patient was catastrophic, especially as she had only one of the five Guillevin CSS mortality associated factors—namely, gastrointestinal involvement.7

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

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

**References**


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**NOTICE**

Dr Barbara Ansell CBE A service of thanksgiving for the life and work of Dr Barbara Ansell will be held on Saturday 16 February 2002 at 11.00 am at Southwark Cathedral, London Bridge. Tickets may be obtained by sending a stamped self addressed envelope to: Memorial Service, British Society for Rheumatology, 41 Eagle Street, London WC1R 4AR. All are welcome to attend.

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Contact: Deborah J Bork, The Cleveland Clinic Foundation, Desk A50, Center for Vasculitis Care and Research, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: 216 445 8533
Fax: 216 445 7569
Email: borkd@ccf.org
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Cryoglobulinaemic vasculitis as presenting manifestation of infective endocarditis

L La Civita, P Fadda, I Olivieri and C Ferri

Ann Rheum Dis 2002 61: 89-90
doi: 10.1136/ard.61.1.89

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