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 β2 glycoprotein 1 (β2GPI) dependence of the aCL was not defined, even though the authors focused on β2GPI independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines the antibodies detected by the classical aCL enzyme linked immunosorbent assay (ELISA).—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 designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominately, β2GPI independent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standards for β2GPI independent assays.

The method for determination of 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 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 immunoglobulins. β2GPI independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for β2GPI dependent aCL on the same plate by adding β2GPI in parallel duplicate wells. The final concentration of β2GPI was 10 μg/ml. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β2GPI. For the final determination of β2GPI dependent binding, the values obtained in wells without β2GPI were subtracted from the values measured in wells with added β2GPI. The patients’ histories were evaluated for the occurrence of arterial or venous thrombosis and recurrent fetal loss. Statistical analysis was performed with the χ² test where appropriate.

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

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>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>
</tr>
<tr>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>NHS (n=53*; n=32†)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>RA (n=33)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=36)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=17)</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

aCL, Anticardiolipin antibodies; β2GPI, β2 glycoprotein 1; NHS, normal human sera; RA, rheumatoid arthritis; RF, rheumatoid factor.

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The editors will decide as before whether also to publish it in a future paper issue.
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, 3/7 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 from 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. RA 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 β2GPI independent aCL do not confer an increased risk for APS in RA.

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References


Authors’ reply

In response to the comments of Ambrozic et al we would like to add some information to the data published earlier in the Annals. The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera containing the dependence of aCL on β2-glycoprotein I (β2GPI) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2GPI in blocking buffer (containing fetal calf sera or bovine serum albumin). In our previous 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 β2GPI. This method justified the terminology of β2GPI independent aCL for sera containing aCL without anti-β2GPI antibodies. The absence of anti-β2GPI antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen all sera.

The concentration of exogenous β2GPI 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 β2GPI in the assays used for the detection of β2GPI dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2GPI) did not react with β2GPI in the other ELISA test specifically designed to detect anti-β2GPI autoantibodies, and therefore which could detect hypothetically high titer of anti-β2GPI 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 tested in microtiter plates using two laboratories. In conclusion, patients with RA may have antiphospholipid antibodies and RA: presence of β2GPI independent aCL. Ann Rheum Dis 2001;60:303–4.


Methotrexate and postoperative complications

Grennan et al report the safety of continued methotrexate in the perioperative period. Previous investigators have despaired of answering this question definitively owing to the difficulty in recruiting subjects. It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of complications.

Despite this important finding, we believe that the results of this study should be regarded with some reservation: continuation of methotrexate throughout the perioperative period should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate related pancytopenia. Indeed, in a community based, observational study of methotrexate use in 460 patients we found the number of normal subjects (blood donors) as previously described. 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-β2GPI and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2GPI test with the nude to positive controls from patients with APS and were used according to previous studies. In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2GPI antibodies in normal serum. 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


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not alter disease control in the vast majority of complications to stop methotrexate one week before surgery. Sudden volume loss, patients with renal impairment (best assessed in the study group. It is important to note that this is made about the prevalence of this in the tertiary referral centre. Renal impairment is an unclear whether Wrightington Hospital is a hazard of methotrexate prescribing in sub-

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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AUTHORS’ RET

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. A 22 year old woman presented with 18 months of a waddling gait disturbance. Hip and back 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 squating and holding her arms above her head.

Investigations showed a mild anaemia secondary to β thalassemia 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 1.08 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, antientomodysial, 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. Osteoporosis was demonstrated by dual emission x ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm² (2.65 SD below the young adult female mean) and the neck of the femur 0.633 g/cm² (2.9 SD below the mean).

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

Within two months there was bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphate reduced to 374 U/l. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm² (mean level for young adult women). and the neck of the femor 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 pseudofractures and Looser’s zones, or secondary hyperparathyroidism evident on bone scan. Most patients were middle aged, and responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates. A recent case finding study of coeliac disease showed that many patients in fact present with non-gastrointestinal symptoms, of which anaemia is the most common. Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area, secondary hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.

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

Early diagnosis of coeliac disease is important because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determination of antigliadin and antientomodysial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%. There is a genetic influence on the susceptibility to coeliac disease, with a 10% prevalence rate among first degree relatives. On screening our patient’s relatives, one of two siblings was also found to have coeliac disease. A strong association has also been found with HLA-DR3 and DR5/DR7.

Treatment with a gluten-free diet with subsequent villous restitution on repeat biopsy has been associated with rapid gains and even normalisation of bone biomarkers; the greater the degree of osteopenia, the more rapid the gain. The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix. Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.

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

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References
1 A Mass AJ, Waterhouse C, Terry R. Gluten-sensitive enteropathy with osteomalacia
Nuclear cells (PBMCs), the site for a host of tissues, particularly peripheral blood mononuclear cells, have been reported to be altered in patients with RA. Plasma and serum levels of zinc (Zn) and copper (Cu) have been reported to be altered in RA and Cu among Indian patients. Plasma and peripheral blood mononuclear cells (PBMCs) could be an interesting site for such studies.

Plasma and PBMCs to see if they correlated with RA could be an interesting site for such studies.

Patients attending the rheumatology clinic at our institute and satisfying the American College of Rheumatology (formerly American Rheumatism Association) criteria for the diagnosis of RA were studied. Patients were categorised as either active or inactive RA. All patients classified as active RA had at least three of the following: morning stiffness for more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. Both plasma and lysed PBMC samples were read on atomic absorption spectrophotometer (Perkin Elmer, Norwalk, CT) at a wavelength of 213.8 nm for Zn and 324.7 nm for Cu. The atomic absorption spectrophotometer was calibrated with reference standards obtained from Sigma Chemicals Company (St Louis, MA).

Thirty nine patients (31 women) with RA had a mean (SD) age of 36.2 (8.3) years (range 18–52) and mean disease duration of 55.8 (36.6) months (range 6–168). Twenty patients had inactive and 19 patients active disease, respectively. Twenty two healthy controls (14 women), well matched for age (mean age 34.2 (6.2) years, range 20–56) with the two patient groups, were studied at the same time. Both patients and controls were of middle socioeconomic status. Table 1 shows the plasma and PBMC levels of Zn and Cu.

Our results are in agreement with earlier studies which showed that plasma Zn levels are significantly lower and plasma Cu levels significantly higher in patients with active RA. Additionally, it is shown here that PBMC levels of these elements have an inverse relation with plasma levels.

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

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

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

It would be premature to speculate about a possible role for supplementation with Zn and Cu for patients with RA. From the results shown in this study, patients with inactive RA had similar levels of 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 a shift back to those seen in controls. Hence, further studies need to be carried out on paired samples in a cohort of patients, once when the disease is active and again when it becomes inactive. Plasma Zn levels decrease with the control of inflammation and attain the levels of controls then there would be no indication for dietary supplementation with these metals.

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 Zn (µg/l)</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>PBMC Zn (µg/10⁶ 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 Cu (µg/l)</td>
<td>1646 (357)</td>
<td>1016 (296)</td>
<td>1426 (324)</td>
<td>946 (446)</td>
</tr>
<tr>
<td>PBMC Cu (µg/10⁶ cells)</td>
<td>58.0 (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 those with inactive RA (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). Overall 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 RA (p<0.01); toverall, patients with RA had lower levels than controls (p<0.01) and those with active RA were lower than those with inactive disease (p<0.01). There was a negative correlation between plasma and PBMC copper levels (p<0.05).

References


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

The relevance of monoclonal gamopathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gamopathy or...
paraproteins can be detected in healthy adults and in different disease entities like amyloidosis, malignant proliferative disorders, associated with hepatitis C infections, and rheumatic diseases. The overall incidence of paraproteins in adults is about 1%. This incidence is higher in people over 70 and increases with age. When a paraprotein is detected and no underlying disease is present, the condition is referred to as a monoclonal gammopathy of undetermined significance.

Owing to their immunological properties, paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the so-called cryoglobulins. When cryoglobulins are detected in the serum of a patient, this finding is usually associated with the coexistence of paraproteins. Recently, three patients with a clinical picture of a necrotising vasculitis associated with an essential cryoglobulinaemia (type 1) were admitted to our department. The causative relationship between the cryoglobulinaemia and the clinical symptoms was reduced by the reduced severity of the clinical signs when paraprotein levels were decreased.

Case reports
Patient A was a 69 year old man who, in May 1999, developed extremely painful purpura of the upper part of the third finger of his left hand. In the following days the upper part of the third finger of his left hand numbness was noticed. In the following days the upper part of the third finger of his left hand. Physical examination showed normal vessels. Immune hand. In the following days the upper part of the third finger of his left hand numbness was noticed. Physical examination showed normal vessels. In the following days the upper part of the third finger of his left hand numbness was noticed. In the following days the upper part of the third finger of his left hand numbness was noticed. In the following days the upper part of the third finger of his left hand numbness was noticed. Laboratory examination showed a paraprotein M component of 4 g/l. 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, 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 symproms are present.


Cryoglobulinaemic vasculitis as presenting manifestation of infective endocarditis
Seromunomological alterations, including antibodies and/or cryoglobulins, are common in infective endocarditis (IE); however, specific autoimmune diseases, 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. The report 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 p&oacute;doxagia. 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 tactile sensations in the fingers and legs; mild ideomotor slowing down; shaky movements; and unsteady gait. An electroencephalographic study recorded a moderate sensorimotor peripheral neuropathy, while ECG showed narrowing of the QRS complexes, mainly cryoglobulinasemia, and comple-

References
as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the clinically prevalent CV symptoms appeared 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” cryoglobulinemia is not uncommon, but only a few studies report IE clinically presenting as CV. This latter presentation can mean a diagnosis more than 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 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 aetiopathogenesis 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 transthoracic echocardiography at the onset, were sufficient reasonably to exclude a suspicion of IE presenting as CV.

In conclusion, CV may represent the presentation 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 clinicomicrobiological evaluation, including transoesophageal echocardiography.

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. \(^1\) We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E, (PGE) administration, which to our knowledge has not been previously reported.

A 25 year old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud’s phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy 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 disease. 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 prednisone, 60 mg/day, was started with prompt improvement in the symptoms.

We investigated the possibility that PGE, mediated cytokine production might be the cause of the relapse of SLE in this patient. Intracellular expression of cytokines in the patient’s T lymphocytes after specific PGE, stimuli (10 ng/ml) was determined by flow cytometry using anticytokine conjugates in combination with surface anti-CD3 (Pharmingen, San Diego, CA), as previously described. \(^7\) The test performed eight months after the PGE, treatment showed a dramatic rise in interleukin 4 (IL4) production (table 1). It has been suggested that cytokines have an important role in the immune dysregulation seen in lupus prone mice and in patients with SLE. Increasing evidence supports a role for T helper cell type 2 (Th2) cytokines, such as IL4, in promoting and perpetuating B cell hyperactivity and autoantibody formation. \(^8\) A change in the proportion of Th2 cytokines might be associated with the polyclonal B cell activation seen in SLE. \(^9\) 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. \(^10\) On the other hand, recent studies it has been suggested that PGE, alters the Th1/Th2 balance of T cells to a dominant Th2 response. \(^11\) We suggest that the rise in IL4 production induced by the PGE, as shown in vitro in this patient, may be a marker of dysregulation of the Th1/Th2 profile and might have been the cause of her lupus relapse.

References


| Table 1 Intracellular cytokine production after PGE2 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 |
|---------------|----------------|----------------|----------------|----------------|
|               | IL2            | INFγ           | IL4            |               |
| Control       | 1.2            | 0.6            | 1.0            | 1.0           |
| Patient       | 1.4            | 0.2            | 1.0            | 0.6           |
| Basal PGE     | 0.8            | 0.8            | 0.6            | 0.6           |
| Basal PGE     | 1.8            | 1.8            | 0.6            | 1.0           |
| Basal IL4     | 1.2            | 1.4            | 1.0            | 1.0           |
| Basal IL4     | 0.8            | 0.6            | 1.8            | 0.6           |
| Basal IL4     | 1.0            | 1.0            | 0.6            | 1.0           |
| Basal IL4     | 1.0            | 1.0            | 0.6            | 1.0           |
| Basal IL4     | 1.0            | 1.0            | 0.6            | 1.0           |

IL2, interleukin; INFγ, interferon γ.
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synonymous concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation. Systolic and serum osteocalcin correlate positively. In ankylosing spondylitis (AS) the serum concentration has been reported to be low or normal.

To answer the question whether serum osteocalcin is a useful marker of disease activity in AS, longitudinal studies may be more sensitive and specific. For this reason changes in serum osteocalcin were correlated with changes in ESR, which is probably still the best marker of inflammation in AS.

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age 43 (11) years; disease duration 14 (9) years) venous blood was taken at the start and end of a three week rehabilitation course consisting of physical exercise, physiotherapy, magnetotherapy, electrotherapy, underwater exercises, and radon treatment as prescribed by the patient’s doctor. Patients were advised not to change their drug treatment. The ESR was determined according to the Wintrobe method, and the result at one occasion being used for calculation. Serum was frozen at −18°C until further analysis. Osteocalcin was measured in one batch with a commercially available kit (IRMA; Boeck, Vienna; normal range according to the manufacturer 7.5–31.5 ng/ml in men, 7.5–31.7 ng/ml in women). Results are given as median (25th, 75th centile). The Mann-Whitney rank sum test and Spearman rank 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, 32.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/1st h, osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR and osteocalcin at the first examination did not correlate significantly (r=0.07; p=0.5). The changes in ESR (1, 4, 6 mm/1st h) and changes in osteocalcin (−0.5 to +2.6, 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.
Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-tap antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.13

Low CD4+ T lymphocyte counts are rare in the absence of immunodeficiency, most commonly infection with HIV.14 In our patient, major histocompatibility complex class II deficiency was excluded by the expression of HLA-DR on peripheral blood lymphocytes. Serological testing for HIV infection was negative and, additionally, the patient had no risk factor for transmission of HIV infection or recent immunosuppressive treatment.

All patients with idiopathic CD4+ T lymphopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4×10⁷/l, to determine the natural history of their infections and lymphocyteopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking.15 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.16 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 hypergammaglobulinaemia.17 Wiskott-Aldrich and Takayasu arteritis have been reported previously.18 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 CD4+ lymphopenia may cause dysgamma-globulinaemia and autoimmunity syndromes such as Takayasu arteritis.

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References

**Figure 1** Magnetic resonance imaging shows dilatation and irregular contour of the descending aorta and narrowing of the abdominal aorta.

**Recurrent orbital pain and diplopia in a 12 year old boy**

A previously healthy 12 year old boy was referred to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia. The first disease manifestation had started three years before, when the patient suddenly presented with diplopia and painful periorbital and eyelid oedema. Limited abduction of the right eye was present. The treating ophthalmologist, after a thorough investigation that excluded brain tumours, orbital masses, and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinus thrombosis are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extracurricular muscles, which is diagnosed by a combination of signs and symptoms, and laboratory tests. Despite the wide range of possible causes for orbital inflammation, it is often difficult to identify a specific cause in a given patient. Orbital inflammation may cause orbital pain, diplopia, and limited or complete ocular motility in some patients. The presence of orbital pain, diplopia, and limited or complete ocular motility in a patient with a history of recurrent ocular pain and diplopia is suggestive of orbital myositis. Orbital myositis is a rare condition that has been reported in both adults and children.19

**Figure 1** Orbital MRI (T1 weighted image with contrast) that shows increased signal intensity and size of the right rectus lateralis muscle.
Hodgkin's lymphoma is rare. System and vertebrae by low grade non-
involved in most cases. When steroids fail to control muscle inflammation, methotrexate and cyclosporin have been used with success. In our patient, cyclosporin was successful as a steroid sparing agent, because a rapid recurrence of symptoms had always occurred in the past when the corticosteroid dose was reduced, and at present, after six months of cyclosporin treatment, the boy is still asymptomatic and receiving a low dose of steroids.

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

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**References**

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

A 71 year old man presented to us in January 2000 with a three month history of severe low back pain affecting mainly the left lumbar area and buttock, radiating to the outer aspect of the left thigh and calf. He did not have bladder symptoms or history of recent falls. On examination, he looked well; there was no lymphadenopathy. He had restricted back movement with tenderness of lower lumbar spinous processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and coordination. Knee jerks were reduced, ankle jerks were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent, both plantar responses were absent. The total white cell count was 3.5×10^9/L (1.0%), basophils 0.0×10^9/L (0.0%), and occasional atypical lymphocytes were seen in blood film. The erythrocyte sedimentation rate was 4 mm/1st h, a myeloma screen was negative, and prostate specific antigen was normal.

In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis but no infiltration. Treatment was started with etidronate and calcium.

Investigations showed normal serum biochemistry apart from a mild increase of alkaline phosphatase, which was 242 IU/L (normal 60–220). The total white cell count was 24.7×10^9/L, differential count showed neutrophils 5.5×10^9/L (14%), lymphocytes 17×10^9/L (69%), monocytes 4.0×10^9/L (16.0%), eosinophils 0.2×10^9/L (1.0%), basophils 0.0×10^9/L (0.0%), and occasional atypical lymphocytes were seen in blood film. The erythrocyte sedimentation rate was 4 mm/1st h, a myeloma screen was negative, and prostate specific antigen was normal.

A lumbosacral spine x ray examination showed biconcave L3 with diffuse osteopenia. Abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotope scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes.

An MRI scan showed extensive infiltration involving vertebral bodies and appondages throughout the lumbosacral spine, being most intense at the biconcave L3; the appearance was consistent with lymphoma or myeloma (fig 1).

During his stay in hospital, the patient's pain resolved completely after treatment with non-steroidal anti-inflammatory drugs, analgesics, and physiotherapy. His haematologist started treatment of the patient with chlorambucil 10 mg/day for 10 days to be repeated every three weeks, these cycles to be continued for 12 months.

Eight months after the diagnosis of spinal lymphoma, the patient has remained well and active; his back pain is minimal.

In rheumatology, it is essential to differentiate between malignant disease and the more common causes of back pain. Our patient was in a good physical condition, which is unusual for someone with malignancy, his presentation with low back pain appeared to be a typical case of sciatica, and the pain settled down with conventional treatment. Clinically there was no evidence of recurrence of lymphoma—for example, enlarged lymph nodes, weight loss, or fever. However, because of his age at presentation and significant past history thorough investigations were mandatory.

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**References**

**Unusual complications in the Churg-Strauss syndrome**
Although abdominal complications are occasionally reported in the Churg-Strauss syndrome (CSS), bowel perforations, cholecystitis, eosinophilic peritonitis, and oophoritis are very unusual and normally resolve after immunosuppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

A 64 year old woman with a 13 year history of urticaria, recurrent rhinitis, and asthma was admitted for abdominal pain. An increasing peripheral eosinophilia rising from 1% to 22% in the past five years was detected. Two years before hospital admission an extensive urticarial erythema developed. An abdominal ultrasonography performed during an asthmatic exacerbation when she had no abdominal pain disclosed a thick-walled gall bladder with no echogenic contents. An excited nasal polyp showed polypoid hyperplasia with many eosinophils.
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 1×10⁹/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 ovarium. A cholecystectomy and right aneucotomy were performed. A month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.9×10⁹/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/hr, 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 proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaluronan and hyalocollagen casts. An abdomen CT scan showed moderate ascites. The ascitic fluid, rich in eosinophils, the ascitic fluid was serofibrinous with a protein concentration of 25 g/l, a leucocyte count of 1.05×10⁹/l, and 22% eosinophils. Abdominal ultrasonography and vascular sonography should be included in the routine screening of patients with CSS.

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

The ascitic fluid, rich in eosinophils, the 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, but has only been confirmed in one case so far.

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

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

REFERENCES


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, WC1R 4AR. All are welcome to attend.
22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
Contact: Professor F.C. Breedveld, Leiden University Medical Centre, Department of Rheumatology, PO Box 9600, 2300 RC Leiden, The Netherlands
Tel: +31 (0)71 526 3598
Fax: +31 (0)71 526 6752
Email: F.C.Breedveld@lumc.nl
Website: www.cwr.org

Tenth Intensive Applied Epidemiology Course for Rheumatologists
11–15 Mar 2002; Manchester, UK
No previous experience in epidemiology is needed. The course is residential and limited to 25 places.
Contact: Ms Lisa McClair, ARC Epidemiology Unit, University of Manchester, Oxford Road, Manchester M13 9PT, UK
Tel: +44 (0)161 275 5993
Fax: +44 (0)161 275 5043
Email: Lisa@f1.ser.man.ac.uk

OMERACT VI
11–14 Apr 2002; Bali
Includes two modules: MRI and economics; and four workshops: patients’ perceptions, imaging (healing), progressive systemic sclerosis, minimally important clinical difference and osteoarthritis.
Contact: Conference Organisers Q2Q, 7 Swann Street, Old Isleworth, Middlesex TW7 6RJ, UK; or Peter Brooks, Faculty of Health Sciences, Level 1, Edith Cavell Building, Royal Brisbane Hospital, Herston 4029, Australia
Fax: +44 208569 9553
Email: tony@q2q.co.uk or p.brooks@mailbox.uq.edu.au
British Society for Rheumatology
XIXth AGM
23–26 Apr 2002; Brighton, UK
Contact: BSR, 41 Eagle Street, London WC1R 4TL, UK
Website: www.rheumatology.org.uk

4th EULAR Sonography Course
25–28 Apr 2002; Madrid, Spain
The course is entitled “Practical use of musculoskeletal ultrasonography”
Contact: Esperanzo Naredo
Email: enaredo@cremas.com
Website: www.eular.org/courses and www.sameint.it/eular

10th International Vasculitis and ANCA Workshop
25–28 Apr 2002; Cleveland, Ohio, USA
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
Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

International Congress: New Trends in Osteoarthritis
9–11 May 2002; Milan, Italy
Contact: Organising Secretariat, O.I.C. S.r.l., Via Fatebenefratelli 19, 20121 Milan, Italy
Tel: +39 02 65 71 200
Fax: +39 02 65 71 270
Email: osteoarthritis@oic.it

10th World Congress on Osteoporosis
10–14 May 2002; Lisbon, Portugal
Contact: IOF Secretariat, 71 cours Albert Thomas, F-69003 Lyon, France
Tel: +33 472 91 41 77
Fax: +33 472 36 90 52
Email: info@iof Lyon.org
Website: www.osteofound.org

5th European Conference on Systemic Lupus Erythematosis
26–30 May 2002; Athens, Greece
Chairman Professor HM Moutsopoulos Secretariat: Amphiphisis Congress Organising Bureau
Email: hmoutsop@med.uoa.gr
Website: congress@amphitrion.gr

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wyss, Executive Secretary EULAR, Witkonkerstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: eular@bluewin.ch
Website: www.eular.org

10th International Congress on Behçet’s Disease
27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behçet’s Disease
Up to eight young investigator awards, each of $500, will be awarded on the basis of abstracts submitted
Contact: Professor Ch C Zoubboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabeckstrasse 60–62, 14195 Berlin, Germany
Fax: +49 30 84456908
Email: zoubbure@zedat.fu-berlin.de
Website: www.userpages.fu-berlin.de/~zoubbure
ISBD website: www.behcet.ws

29th Scandinavian Congress of Rheumatology
15–18 Aug 2002; Tromso, Norway
Contact: Hans Nossent, Department of Rheumatology, University Hospital Tromso, Norway
Tel: 47 776 27294
Fax: 47 776 27238
Email: 29scr2002@rito.no or reevan@rito.no

Translational Research in Autoimmunity
21–22 Sep 2002; Pavia, Italy
Contact: Organising secretariat: eventi S.R.L., Corso Cavour, 18/20 - 27100 Pavia, Italy
Email: tra@c20pr.com
Website: www.e20pr.com
Congress website: www.medicine.ucsd.edu/ albani/2001 meeting

OsteoArthritis Research Society International (OARSI) World Congress
22–25 Sep 2002; Sydney, Australia
Contact: OsteoArthritis Research Society International (OARSI), 2025 M Street, NW, Suite 800, Washington DC 20036, USA
Tel: +1 202 367 1177
Fax: +1 202 367 2177
Email: oars@oarsi.org
Website: www.oarsi.org

10th International Congress on Antiphospholipid Antibodies
29 Sep–3 Oct 2002; Sicily, Italy
Deadline for abstracts 1 April 2002
Contact: Secretariat, 10th International Congress on Antiphospholipid Antibodies, c/o Kenes International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 5140018/9
Fax: 972 3 5140077 or 972 3 5172484
Email: aps@kenes.com
Website: www.kenes.com/aps

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases
14–17 Oct 2002; Nashville, Tennessee, USA
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA
Tel: (615) 343 7329
Fax: (615) 343 7534
Website: www.eicosanoids.science.eayne.edu

66th American College of Rheumatology AGM
25–29 Oct 2002; New Orleans, USA
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 250, Atlanta, Georgia 30045–4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@rheumatology.org
Website: www.rheumatology.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis
7–9 November 2002; Barcelona, Spain
Contact: Yolande Pletier Communication, Boulevard Kleyer 108, 4000 Liège, Belgium
Tel: 32 4 254 12 25
Fax: 32 4 254 12 90
Email: ypc@compuserve.com

Certifying Examination in Pediatric Rheumatology
18 Nov 2002
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA
Tel: 919 929 0461
Fax: 919 918 7114 or 919 929 9255
Website: www.abp.org

Future EULAR congresses
18–21 June 2003, EULAR 2003 Lisbon, Portugal
9–12 June 2004; EULAR 2004 Berlin, Germany
8–11 June 2005; EULAR 2005 Vienna, Austria
21–24 June 2006; EULAR 2006 Amsterdam, The Netherlands

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