Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled “Antiphospholipid antibodies and RA: presence of β2GPI independent aCL” by Bonnet et al published in the Annals in March 2001. 1 We believe that the letter needs additional clarification owing to inconsistencies in the terminology, methodology of antiphospholipid antibody (aPL) detection, and determination of positive values.

The use of the term “anticardiolipin antibodies” was somewhat misleading. The term was introduced and abbreviated as “aCL,” a group of antibodies detected in many conditions, but the β2 glycoprotein 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 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.2 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, if the sera containing high titres of anti-β2GPI might have yielded positive results by the method described in the letter.

The definition of antibody units in the letter is not clear and using Harris's standards for β2GPI independent aCL is not appropriate. With the use of Harris's standards,2 the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined.3 However, Harris’s standards were designed for use in the classical aCL ELISA and were prepared by pooling serum samples from patients with APS. Therefore, they contain mainly, or predominantly, β2GPI dependent aCL. β2GPI independent aCL were not defined in those standards and they were not meant as standards for β2GPI independent assays.

The interpretation of 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 recognised β2GPI associated with cardiolipin. We reported this binding pattern for anti-β2GPI in children with atopic dermatitis,4 and the same was shown also for some patients with autoimmune diseases, including APS.5 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 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.2 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, if the sera containing high titres of anti-β2GPI might have yielded positive results by the method described in the letter.

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

<table>
<thead>
<tr>
<th>No of positive samples:</th>
<th>Anti-β2GPI*</th>
<th>β2GPI dependent aCL</th>
<th>β2GPI independent aCL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
<td>IgM</td>
<td>Any Ig</td>
</tr>
<tr>
<td>NHS (n=53, n=32†)</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>RA (n=33)</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=36)</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RA-RF (n=17)</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

*Anti-2GPI antibodies, β2GPI, β2 glycoprotein I, NHS, normal human sera, RA, rheumatoid arthritis, RF, rheumatoid factor.
any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2GP1 and β2GP1 dependent aCL of IgA isotype. Interestingly, 9/11 RA sera which showed binding to β2GP1 adsorbed on a high binding plate did not recognise β2GP1 associated with cardiolipin, as already reported.2 In contrast, 3/9 RA sera binding to β2GP1 complexed with cardiolipin did not recognise β2GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2GP1 in RA, which may differ in fine specificity from anti-β2GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β2GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β2GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2GP1 (10 µg/ml) lowered the binding of β2GP1 independent aCL by about 50%, most probably owing to the competition between β2GP1 independent aCL and β2GP1 for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2GP1 and β2GP1 dependent aCL, which might be associated with the signs of APS. The importance of distinguishing β2GP1 independent aCL in APS has not been fully clarified. It seems likely that the 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.3

The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera. The dependence of aCL on β2-glycoprotein 1 (β2GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2GP1 in blocking buffer (containing fetal calf sera or bovine serum albumin). In our former solution we did not contain bovine or calf sera but only purified bovine serum albumin. So, this method was adapted to detect antibodies directed against cardiolipin antigen alone and not against the complexes of cardiolipin bound to exogenous β2GP1. This method justified the terminology of β2GP1 independent aCL for sera containing aCL without anti-β2GP1 antibodies. The absence of anti-β2GP1 antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen all sera.

The concurrence of β2GP1 contained in human serum is not significant at a 1/100 dilution (the dilution employed to screen our sera), in comparison with the 10% of calf sera added to the test as source of exogenous β2GP1 in the assays used for the detection of β2GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2GP1) did not react with β2GP1 in the other ELISA test specifically designed to detect anti-β2GP1 autoantibodies, and therefore which could detect hypothetically high titres of anti-β2GP1 antibodies contained in these sera.

Harris’s standards were used after calibration of our positive control sera from patients with proven antiphospholipid syndrome (APS), which we used for the positive controls in every microtiter plate. We used these for the detection of aCL in our previous studies employing ELISA test without bovine or calf sera.4 The antiphospholipid antibodies, including aCL, are directed against several anti-genetic 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 as a reagent of the VDRL test. These reagents were constituted by lipids alone without any other cofactor such as β2GP1. So, Harris’s standard can also be used to detect aCL directed only against phospholipid and not against the complex β2GP1-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 β2GP1 used in our assay was provided by Stago laboratories (Asnière, France) and was purified from human sera. We used sodium dodecyl sulphate-polyacrylamide gel electrophoresis and western blotting to ensure that this purified protein was not contaminated.

For every antibody determination, aCL and anti-β2GP1 autoantibodies, normal levels were established from studies of a large number of normal subjects (blood donors) as previously described.5 In this study, 70 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-β2GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2GP1 test were prepared to positive controls from patients with APS and were used according to previous studies.6,7

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2GP1 antibodies in normal sera. The percentage of positive normal serum samples was <3%. These differences between our results and those of Ambrozic et al are probably associated with a differing sensitivity and specificity of the methods between the two laboratories.

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References


Methotrexate and postoperative complications

Grennan et al report the safety of continued methotrexate in the perioperative period.' Previous investigators have despised 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 early complications. Despite this important finding, we believe that the results of this study should be regarded with some reservation: continuation of methotrexate throughout the perioperative period should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate related pancyclopaenia.18 Indeed, in a community-based, observational study of methotrexate use in 460 patients we found the
perioperative period to be especially hazardous for patients with renal impairment and sepse. Two subjects developed pancycopenia under these conditions, one of whom died. Although all consecutive patients were included in the study by Grennan et al., it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made about the prevalence of this in the study group. It is important to note that this is a study of methotrexate use in elective surgery.

We suggest caution should be taken in patients with renal impairment (best assessed by creatinine clearance) and in the elderly with comorbid cardiovascular disease when approaching surgery. Sudden volume loss, bleeding, or dehydration will impair methotrexate excretion and increase the risk of bone marrow toxicity in this group. It may be prudent in those assessed as at high risk of this complication to stop methotrexate one week before the operation and restart treatment one or two weeks after the operation, depending on postoperative progress. This time period without methotrexate treatment will not lose disease control in the vast majority of patients, although after four weeks without treatment, most will have a flare of the disease.1

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References

Authors’ reply
Dr Wluka draws attention to the potential hazard of methotrexate prescribing in subjects with chronic renal failure and sepsis, and we would not disagree with this point. The risk of surgery is increased by any coincidental medical disease including renal failure and sepsis as well as chronic vascular disease. We noted this in our study. The role of the doctor/rheumatologist is to ensure that any such chronic medical problems are under optimal control before elective orthopaedic surgery. Methotrexate treatment should not be withdrawn from patients with rheumatoid arthritis if the disease is well controlled before elective surgery. The comments of Dr Wluka do not invalidate this conclusion.

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LETTERS

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

It is rare for coeliac disease to present only with symptoms of osteomalacia, without the classic symptoms of diarrhoea, steatorrhoea, and abdominal discomfort.1–3 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 β thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphatase of 1375 U/l (normal 30–120 U/l), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.0 mmol/l (0.8–1.4 mmol/l), 25-hydroxy vitamin D <5 nmol/l (15–110 nmol/l), and raised parathyroid hormone 53.1 pmol/l (1.0–6.5 pmol/l). Investigations were carried out for a malabsorption syndrome. Antigliadin, antiendomysial 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 her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphatase reduced to 374 U/l. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm2 (mean level for young adult women), and the neck of the femur by 39% to 0.878 g/cm2 (0.8 SD below the mean). She had also gained more than 7 kg in weight, and repeat gastroscopy and duodenal biopsy were normal.

Osteomalacia is now an uncommon disease, and even more uncommon is the presenting symptom of coeliac disease. Since its first description in 1965,1 there have been several more 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.2 Most patients were middle aged or 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.1 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 to small bowel atrophy, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.3

Secondary hyperparathyroidism can develop if it did in this case presenting increased bone turnover.4 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 antiantiendomysial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.6 They are 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 biomarkers; the greater the degree of osteopenia, the more rapid the gain.8 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.8 Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.5

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 this treatment including vitamin D may lead to rapid and effective recovery.4

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

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

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

Patients attending the rheumatology clinic at our institute and satisfying the American College of Rheumatology (formerly American Rheumatism Association) criteria for the diagnosis of RA were studied. Patients were categorised as either active or inactive RA. All patients classified as active RA had at least three of the following: morning stiffness for more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. Both plasma and 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 a mean (SD) age of 36.2 (8.2) years (range 20–56) and mean disease duration of 213.8 (66.8) months (range 6–168) were studied. 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.

## Table 1

<table>
<thead>
<tr>
<th>Plasma zinc (µg/l)*</th>
<th>687 (467)</th>
<th>982 (264)</th>
<th>824 (386)</th>
<th>1024 (428)</th>
<th>1024 (428)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC zinc (µg/10⁶ cells)†</td>
<td>135.2 (28.6)</td>
<td>108.3 (38.4)</td>
<td>121.1 (34.4)</td>
<td>98.4 (16.4)</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>
<td>946 (446)</td>
</tr>
<tr>
<td>PBMC copper (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>
<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 among patients than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). Overall there was a 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<0.01) and those with active RA had lower levels than those with inactive disease (p<0.01). There was a negative correlation between plasma and PBMC copper levels (p<0.05).

References
paraproteins in adults is about 1%.

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 deduced by the reduced severity of the clinical signs when paraprotein levels were decreased.

Case reports

Patient A was a 69 year old man who, in May 1999, developed extremely painful purpura of the upper part of the third finger of his left hand. In the following days the upper part of his finger became necrotic. Angiography of his hand showed the presence of 8 g/l of an M component (IgG 1.2 g/l, IgA 0.08 g/l, and IgM 0.08 g/l). Further laboratory examination showed no abnormalities. Virus serology showed on a positive cytomegalovirus titre. She was treated with chlorambucil 8 mg daily, 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 cryoglo-

dulins. 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 mono-
clonal immunoglobulin. When the serum concentration of the paraproteins was re-
duced, the disease symptoms in our patients improved. These cases suggest that a parapro-
tein found in patients with a rheumatic syndrome is not only indicative of a develop-
ing 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 symp-
toms are present.

References


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 clinically prevalent CV symptoms and signs are in keeping with the patient’s history, and the presence of typical CV signs and symptoms are essential for the timely detection of IE. In case the clinical features are atypical, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinical microbiological evaluation, including transesophageal echocardiography.

In our patients we can reasonably exclude the possibility that IE represented a complication of 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 and signs are in keeping with the patient’s history, and the presence of typical CV signs and symptoms are essential for the timely detection of IE. In case the clinical features are atypical, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinical microbiological evaluation, including transesophageal echocardiography.

ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hyaluronic acid, plicamycin, allopurinol, and propylthiouracil. 

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

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease. We retrospectively examined 35 serum samples from patients with Graves’ disease. Diagnosis of the disease was based on typical signs and symptoms of hyperthyroidism, raised serum triiodothyronine and thyroxine, very low or undetectable thyroid stimulating hormone, and increased thyroid radioactive iodine uptake. All patients had been receiving treatment with carbimazole (30–45 mg) for at least two months. None of the patients were treated with propylthiouracil or any drug affecting the immune function. ANCA antibodies were determined by indirect immunofluorescence (IF) on ethanol fixed granulocytes, as described elsewhere.

Staining patterns were described as cANCA, when a diffuse granular cytoplasmatic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed and as xANCA when a distinct, homogeneous, non-granular cytoplasmatic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Orgentec) as described elsewhere. Hospital Universitari Germans Trias i Pujol is a 533 bed hospital situated on the outskirts of Barcelona. It is a referral hospital serving a population of 700 000 inhabitants. The immunology laboratory is a reference centre.

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

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

References

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 have been reported by Haapala et al, who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and 16 with thyroid disorders. There is a need to determine the aetio-pathogenetic role of ANCA antibodies in Graves’ disease, the precise relation between ANCA and antithyroid drugs and, lastly, the antigens which are responsible for the ANCA positivity. ANCA positivity in Graves’ disease may be attributable to either antithyroid drugs (thiamazole or propylthiouracil) or to the disease itself.

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

References

Table 1 Intracellular cytokine production after PGE1, 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

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE, %</td>
<td>0.8</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>PGE, %</td>
<td>0.6</td>
<td>0.6</td>
<td>10.8</td>
</tr>
</tbody>
</table>

IL2, interleukin 2; INFγ, interferon γ.

Whole blood was incubated with or without PGE1, 10 μg/ml, for six hours in the presence of Brefeldin A. Cells were stained with FITC-anti-CD3, anti-CD25-PE, and anti-IL2-FITC, and then permeabilised, with the phycoerythrin conjugated anti-IL2. Samples were analysed by flow cytometry.
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

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

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

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; mean age (SD) 47.1 (11) years; disease duration 11 (9) years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, hydrotherapy, electrotherapy, underwater exercises, and racquet treatment as prescribed by the patient's doctor. Patients were advised not to change their drug treatment. The ESR was determined according to the Westergen. The result at one hour was 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 manufacturers 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 of 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, serum osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR serum osteocalcin at the first examination did not correlate significantly (r = 0.07; p > 0.5). The changes in ESR (1, 6, 6 mm/1st h) and changes in osteocalcin (−0.5, −2.6, 5.7) ng/ml showed a significant correlation (r = −0.28, p = 0.001).

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.

Table 1 Immunological data of the patient

<table>
<thead>
<tr>
<th>Values</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count (x10³/μl)</td>
<td>1.5</td>
<td>&gt;2</td>
</tr>
<tr>
<td>IgG [g/l]</td>
<td>23.3</td>
<td>(8.4–19.4)</td>
</tr>
<tr>
<td>IgM [g/l]</td>
<td>6290</td>
<td>(620–3980)</td>
</tr>
<tr>
<td>CD3 [x10³/μl]</td>
<td>3.1</td>
<td>0.2–4.2</td>
</tr>
<tr>
<td>CD4 [x10³/μl]</td>
<td>2.0</td>
<td>0.3–2.0</td>
</tr>
<tr>
<td>CD8 [x10³/μl]</td>
<td>1.0</td>
<td>0.3–1.8</td>
</tr>
<tr>
<td>CD19 [x10³/μl]</td>
<td>0.3</td>
<td>0.2–1.6</td>
</tr>
<tr>
<td>CD3/CD16+CD56 [x10³/μl]</td>
<td>0.2</td>
<td>0.1–0.9</td>
</tr>
</tbody>
</table>

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M Herold
University Hospital, Innsbruck Austria
Correspondence to: Dr Falkenbach

References

Takayasu arteritis
Takayasu arteritis is a chronic inflammatory vasculitis that occurs primarily in young women. It occurs world wide, with greatest prevalence in Asian populations. It mainly affects the aorta and its major branches. The Centres for Disease Control and Prevention have broadly defined idiopathic CD4+ T lymphocyte topospecific reaction in the absence of HIV infection or other known causes of immunodeficiency. The report of the ASAS Working Group. J Rheumatol 1999;26:951–96.
been reported previously.

lysophosphatidylcholine; taurine; ethanolamine; and acetylglycerylphosphorylcholine.

CD4+ lymphopenia may cause dysgammaglobulinemia and autoimmune syndromes such as Takayasu arteritis.

S Sebnem Kilic, Ö Bostan, E Çil
Uludag University Medical Faculty, Department of Paediatrics, Görükle, Bursa 16059, Turkey

References

Recurrent orbital pain and diploia 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 diploia. The first disease manifestation had started three years before, when the patient suddenly presented with diploia and painful periorbital and eyelid oedema. Limited abduction of the right eye was present. The treating ophthalmologist, after a thorough investigation that excluded brain tumours, orbital masses, and myasthenia gravis, prescribed naproxen (20 mg/kg/day) and systemic corticosteroid treatment (prednisone 1 mg/kg/day, tapered and withdrawn after 15 days); symptoms recovered completely in two weeks. A first magnetic resonance imaging (MRI) scan of the orbit had shown first degree exophthalmus of the right eye and oedema and thickening of the right rectus lateralis muscle (fig 1). Since then the boy had many episodes of ocular pain and diploia, lasting from two to four weeks, affecting both eyes or alternatively the right and the left, at intervals of up to three months. No sequelae were detected after each relapse. During the last relapse in October 1999, naproxen and high dose oral corticosteroid treatment (prednisone 2 mg/kg/day) were required to control the disease activity, which subsided over a period of two months. After a short period of well-being, the disease flared up again, and recurrence of orbital pain and diploia 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, anticardiolipin, antitissue transglutaminase, antithyroid peroxidase) were unreactive. Other markers that are considered measures of disease activity in juvenile idiopathic inflammatory myopathies were evaluated: factor VIII related antigen levels were raised, while neopterin levels and the number of circulating B lymphocytes (CD19 positive cells) were normal. Electrocardiography and two dimensional echocardiography excluded a concurrent myocarditis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (Scl), Crohn's disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extrinsic and of the right medial rectus muscles. Electromyography showed increased insertional activity, fibrillations, and positive sharp waves. Ocular myositis was diagnosed. The oral prednisone dose was raised to 30 mg/day, and rapidly tapered after improvement of signs and symptoms. In November 2000, cyclosporin (3 mg/kg/day) was introduced; no relapse of the ocular findings has been seen so far, and prednisone has been progressively reduced to the current dose of 5 mg/day.

The group of idiopathic inflammatory myopathies encompasses a variety of common and uncommon syndromes. The uncommon variants of myositis include orbital myositis, a condition that is rare in adults and even rarer in children. Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, Scl, giant cell myocardiitis, 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 oculodystrophies; 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 extraocular...
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 evidence of chronicity of lower limb spinal processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and coordination. Knee jerks were reduced, ankle jerks were absent, both plantars were down going, and there was no sensory deficit. He had a past history of epilepsy, which was controlled by phenytoin and phenobarbitone. In 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypersplenism. Splectomy was performed in 1994, his blood count returned to normal, and repeated full blood counts were stable. In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis but no infiltration. Treatment was started with etidronate and calcium.

Investigations showed normal serum biochemistry apart from a mild increase of alkaline phosphatase, which was 242 IU/1 (normal 60–220). The total white cell count was 24.7x10⁹/l, differential count showed neutrophils 3.5x10⁹/l (14%), lymphocytes 17x10⁹/l (69%), monocytes 4.0x10⁹/l (16.0%), eosinophils 0.2x10⁹/l (1.0%), basophils 0.0x10⁹/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 lumbarosacral spine x ray examination showed biconcave L5 with diffuse osteopenia. Abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotopic scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes.

An MRI scan showed extensive infiltration involving vertebral bodies and appendages throughout the lumbosacral spine, being most intense at the biconcave L5; the appearance was consistent with lymphoma or myeloma (fig 1).

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

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

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

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References

5 Rider LG, Targoff IN. Muscle diseases. In: Miller FW, ed. Classification and presentation and significant past history thorough investigations were mandatory.

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References


Unusual complications in the Churg-Strauss syndrome

Although abdominal complications are occasionally reported in the Churg-Strauss syndrome (CSS), bowel perforations, cholecystitis, eosinophilic peritonitis, and oophoritis are very unusual3 and normally resolve after immunosuppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

A 64 year old woman with a 13 year history of urticaria, recurrent rhinitis, and asthma was admitted for abdominal pain. An increasing peripheral eosinophilia rising from 1% to 22% in the past five years was detected. Two years before hospital admission an extensive urticarial erythema developed. An abdominal ultrasonography performed during an asthmatic exacerbation when she had no abdominal pain disclosed a thick-walled gall bladder with no echogenic contents. An excised nasal polyp showed polypoid hyperplasia with many eosinophils.
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was 1x10^9/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed acalculous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right anexectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.9x10^9/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 antibodies were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaline and hyaline granular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 55 g/l, a leucocyte count of 1.0x10^9/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovarian histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyposis.

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, 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 18.1x10^9/l with 1% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to 435 IU/ml. Purulent fluid in the peritoneal cavity and two perforations in the ileal wall were found. Bowel histology showed wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophilic infiltrates. Granulomas were not found. E coli grew from the peritoneal fluid. Intravenous metronidazole and gentamicin were started. Four days later a new perforation was suspected and a third laparotomy was done, showing a perforated necrotic small bowel plaque. A broad bowel resection was performed but the patient’s evolution was complicated with high fever, ileus, and vomiting, and she died 48 hours later. A necropsy was not allowed.

Abdominal pain is reported in up to 29–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described, the last of these being responsible for up to 10% of the CSS deaths. Acalculous cholecystitis, although very rare, may be the first and sometimes the unique manifestation of the CSS. Its evolution is usually toplid, 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 oварian involvement.

The ascitic fluid, rich in eosinophils, the eosinophilic infiltration of major omentum and peritoneum, and serum astfosis and ESR factors in polyarteritis nodosa and Churg-Strauss syndrome. Medicine (Baltimore) 1999;78:26–37.


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.

FORTHCOMING EVENTS

3rd International Congress on Autoimmunity

20-24 Feb 2002; Geneva, Switzerland

Contact: Professor Yehuda Shoenfeld, 3rd International Congress on Autoimmunity, PO Box 50006, Tel Aviv 61500, Israel

Tel: 9723 614 0018
Fax: 9723 517 5674
Email: autoimm2@kenes.com

www.annrheumdis.com
22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
Contact: Professor F C Bredveld, 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.Bredveld@lumc.nl
Website: www.eurr.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@fs1.ser.man.ac.uk
Website: www.manchester.ac.uk/arc/epi

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 6JR, UK; or Peter Brooks, Faculty of Health Sciences, Level 1, Edith Cavell Building, Royal Brisbane Hospital, Herston 4029, Australia
Fax: +61 440 208569 9553
Email: tony@q2q.co.uk or p.brooks@mailbox.uq.edu.au
Website: www.omeract.org

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 April 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.nl/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.clevelandclinemed.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@oit.it

10IF 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@ioflyon.org
Website: www.osteofound.org

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

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
Contact: Fred Wyss, Executive Secretary EULAR, Wilkononserstrasse 15, CH-8032, Zurich, Switzerland
Tel: +41 1 383 9690
Fax: +41 1 383 9810
Email: eular@bluestein.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 Zouboulis, Department of Dermatology, University Medical Centre Benjamin Franklin, The Free University of Berlin, Fabekstrasse 60–62, 14195 Berlin, Germany
Fax: 49 30 84456908
Email: zoubbere@zedat.fu-berlin.de
Website: www.userpages.fu-berlin.de/~zoubbere
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 27258
Email: 29scr2002@rito.no or revhan@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/2001meeting

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: oarsi@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
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: Volande Plettic Communication, Boul-evard 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: 919 929 1141 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