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

The method for determining cut off values was not explained and the number of normal human sera (NHS) included in the study as negative controls was not given. From the data presented in the letter, one may conclude that the cut off values were arbitrarily set at 20 units both for IgG and IgM isotypes of β2GPI independent aCL and for anti-β2GPI. We recently compared the sensitivity of anti-β2GPI ELISA and classical aCL ELISA. The results showed great differences between their sensitivities and therefore also between the cut off values calibrated by the same standards. In addition, the authors did not report the proportion of NHS positive for each assay and the values of positive samples compared with patients with RA. Instead, they just referred to one study, which is only one of the several published estimations of aPL in healthy subjects.

We would like to support our criticism by adding some data about aPL in our patients with RA. We randomly selected 53 serum samples from patients fulfilling the ARA criteria for RA and 53 NHS as negative controls. The samples were tested for anti-β2GPI, β2GPI dependent aCL, and β2GPI independent aCL. The assays were calibrated with β2GPI dependent monoclonal aCL (IgG and IgM anti-β2GPI ELISA and β2GPI dependent aCL ELISA) and positive in-house standards (all IgA assays and β2GPI independent aCL). The cut off values for anti-β2GPI were set as described by calculating the mean + 2 SD of 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 immunoglobulin. 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...
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, 5/11 RA sera which showed binding to β2GP1 adsorbed on a high binding plate did not recognise β2GP1 associated with cardiolipin, as already reported.8 In contrast, 3/9 RA sera binding 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 for 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 antibodies 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 has not been fully clarified. It seems that β2GP1 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 make clarification to the data published earlier in the Annals.9

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 β, glycoprotein 1 (β2GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) using exogenous β2GP1 in blocking buffer (containing fetal calf sera or bovine serum albumin). In our study, our 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 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 concentration of exogenous 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 ELISA without addition of exogenous β2GP1) did not react with purified β2GP1 in the other ELISA test specifically designed to detect anti-β2GP1 autoantibodies, and therefore which could detect hypothetically high tities 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 were used for 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.7 The antiphospholipid antibodies, including aCL, are directed against several anti- genic targets. Among them, some epitopes are located on the cardiolipin alone. These data published earlier in the literature confirmed the results reported by Stago laboratories (Asniere, France) and were used according to previous studies.10

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-β2GP1 antibodies in normal sera. Whether 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.10 Previous investigators have despaired of answering this question definitively owing to the difficulty in recruiting subjects.11 It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of complications.12

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 may be accompanied by significant complications.13 The elderly and those with renal impairment are at increased risk of methotrexate related pancytopenia.14 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.15 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 a 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 from positive controls from patients with APS and were used according to previous studies.16

Indeed, in a community based, observational study of methotrexate use in 460 patients we found the...
perioripperiod period to be especially hazardous for patients with renal impairment and sepsis. Two subjects developed pancytopenia under these conditions, one of whom died.

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

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

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References

Authors’ reply
Dr Wukka draws attention to the potential hazard of methotrexate prescribing in sub-

jects 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 Wukla 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. 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, antiantiendomysial, and antiglutaminase antibodies were strongly positive, and a small bowel biopsy showed almost total villous atrophy, confirming the diagnosis of coeliac disease. A bone scan demonstrated increased activity throughout the skeleton, consistent with secondary hyperparathyroidism. Osteoporosis was demonstrated by dual emission x ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/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, daily calcium carbonate 600 mg twice a day, slow release ferrous sulphate 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 gastrointestinal and duodenal biopsies 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 pseudofragments and Looser’s zones, or secondary hyperparathyroidism evident on bone scan.2 Most patients were middle aged women, responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates.3 A recent case finding study of coeliac disease showed that many patients in fact present with non-gastrointestinal symptoms, of which anaemia is the most common.4

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

Secondary hyperparathyroidism can develop if it did in the case we report, causing increased bone turnover.6 Low bone mineral density is probably due to a combination of hypocalcaemia, impaired bone mineralisation, and reduced exercise because of skeletal pain and proximal weakness.7

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%.8 9 There is a genetic influence on the susceptibility to coeliac disease, with a 10% prevalence rate among first degree relatives. On screening our patient’s relatives, one of two siblings was also found to have coeliac disease. A strong association has been found with HLA-DR3 and DR5/DR7.10

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.11 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.12 An introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.13

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 methotrexate therapy including vitamin D may lead to rapid and effective recovery.4

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

Plasma and serum levels of zinc (Zn) and copper (Cu) have been reported to be altered in patients with rheumatoid arthritis (RA). 1,3 Few studies have measured these levels in tissues, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of enzymes, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of enzymes, particularly peripheral blood mononuclear cells (PBMCs), the site for a host of enzymes, particularly peripheral blood mononuclear cells (PBMCs). 7 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. 3 Patients attending the rheumatology clinic at our institute and satisfying the American College of Rheumatology (formerly American Rheumatism Association) criteria for the diagnosis of RA were studied. 3 Patients were categorised as either active or inactive RA. All patients classified as active RA had at least three of the following: morning stiffness for more than 45 minutes, five swollen joints, five tender joints, and erythrocyte sedimentation rate (Westergren) more than 45 mm/1st h. 8 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 18–66). 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. 1,3 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. 3 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. 3 The reduced levels in PBMCs may signify a movement of Cu from PBMCs to the liver where it is absorbed and attached to caeruloplasmin. Thus the findings of plasma and PBMC Cu levels may merely be a reflection of an acute phase response, and the alterations may be due to increased hepatic synthesis of caeruloplasmin. The effect of concomitant drugs 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 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. If 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. Results are given as mean (SD)

<table>
<thead>
<tr>
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<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Plasma Cu (µg/dL)</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>Plasma Zn (µg/dL)</td>
<td>130 (28.6)</td>
<td>1083 (38.4)</td>
<td>1214 (34.4)</td>
<td>984 (16.4)</td>
</tr>
<tr>
<td>Plasma Zn (µg/10^3 cells)</td>
<td>1646 (357)</td>
<td>1016 (296)</td>
<td>1426 (324)</td>
<td>946 (446)</td>
</tr>
<tr>
<td>Plasma Cu (µg/10^3 cells)</td>
<td>580 (43.2)</td>
<td>864 (33.2)</td>
<td>743 (38.2)</td>
<td>1042 (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.

References

2. Zoli A, Alomonte L, Caricchio R, Galassi A, Mirone L, Ruffini MP, et al. Serum zinc and copper in active rheumatoid arthritis: Cu 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.
paraproteins in adults is about 1%. 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 shown 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 hand became necrotic. Angiography of his hand was obtained. In the following days the upper part of the third finger of his left hand showed no evidence for vasculitis, but thrombosis associated with classification of the 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 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 sympoms are present.

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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, together with their transient favourable response to corticosteroids (case 2), further delayed the detection of IE responsible for the fatal outcome. Previous reports (Medline) show that the association of IE with “asymptomatic” cryoglobulinaemia is not uncommon, but only a few studies report IE clinically presenting as CV. This latter presentation can mean a misdiagnosis; moreover, steroid treatment can contribute to masking and worsening of the underlying infectious disorder.

In our patients we can reasonably exclude the possibility that IE represented a complication of the CV. In over 300 of our patients with CV, bacterial manifestations have rarely been seen, even in subjects undergoing steroid or immunosuppressive treatments, or both. Moreover, the CV seen in our two patients had quite unusual clinical and virological characteristics: absence of HCV or other hepatotropic viruses; the presence of particularly severe skin purpura; and the presence of neuropathy as important organ involvement. The 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 aetiology of which is still unclear. In a considerable number of patients with CV 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 of 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 presenting manifestation of IE, a life threatening condition for which a timely correct diagnosis and adequate treatment are essential. In patients with CV unrelated to HCV infection and with fever unresponsive to steroids it is strongly recommended that other less common, infectious factors are excluded. IE, for example, should be excluded by repeated blood cultures and careful clinicmicrobiological evaluation, including transoesophageal echocardiography.

### References


ANCA antibodies in Graves’ disease

Several drugs have been associated with antineutrophil cytoplasmic antibodies (ANCA) positivity—namely, hydralazine, penicillamine, allopurinol, and propylthiouracil. Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis, other antithyroid drugs, such as carbimazole and thiamazole, have been linked. Furthermore, ANCA positivity has been described in the course of Graves’ disease without vasculitis.

This study aimed at determining the frequency and specificity of ANCA in a series of patients with Graves’ disease. 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 cytoplasmic staining with central accentuation was seen, as pANCA, when a perinuclear pattern was observed, and as xANCA when a distinct, homogeneous, non-granular cytoplasmic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; 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 Aelistra et al, who reported ANCA positivity by IF in 6/21 (29%) patients with Graves’ disease. The IF staining pattern was cANCA in five cases and xANCA in one case. Anti-MPO 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.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease duration (weeks)</th>
<th>Purpura</th>
<th>Weakness</th>
<th>Arthritis</th>
<th>Hepatitis</th>
<th>Neutrophilia</th>
<th>Neurological involvement</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>7</td>
<td>Haemorrhagic papular nodular</td>
<td>Severe</td>
<td>Recurrent</td>
<td>Absent</td>
<td>Absent</td>
<td>Peripheral + central</td>
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<tr>
<td>2</td>
<td>75</td>
<td>9</td>
<td>Haemorrhagic nodular</td>
<td>Milder-moderate</td>
<td>Constant</td>
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<td>Absent</td>
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<tr>
<th>Patient</th>
<th>ESR (mm/1st h)</th>
<th>CRP (mg/l)</th>
<th>WBC (× 10^3/l)</th>
<th>Neutrophils (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83</td>
<td>53</td>
<td>89 000</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>41</td>
<td>83 600</td>
<td>81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lymphocytes (%)</th>
<th>γ-Globulinemia (g/l)</th>
<th>RF (normal ≤ 20 IU/ml)</th>
<th>C3 (normal 500–1200 mg/l)</th>
<th>C4 (normal 200–550 mg/l)</th>
<th>Cryocrit, % (cryo-type)</th>
<th>Hepatitis virus markers*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>9.5</td>
<td>575</td>
<td>390</td>
<td>&lt;60</td>
<td>0.5 (IgG-IgM)</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>21.3</td>
<td>137</td>
<td>790</td>
<td>100</td>
<td>2 (IgG-IgM)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*HbsAg, anti-HBs, anti-HBc IgM, anti-Hbc, anti-HCV by ELISA and RIBA; anti-EBV IgM, anti-HIV.
MPO in 19 patients, three with vasculitis and who found antibodies against both TPO and ANCA and antithyroid drugs and, lastly, the ANCA that are responsible for the ANCA positivity. ANCA positivity in Graves’ disease may be attributable to either antithyroid drugs (thi-azolole or propylthiouracil) or to the disease itself.

References

This study was sponsored by a grant from the Cata-

Acknowledgment

This study was sponsored by a grant from the Cata-

PostScript

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

A variety of abnormalities in cytokine produc-

References

There is a need to determine the actio-

Table 1 Intracellular cytokine production after PGE, stimulation in the patient and in an asymptomatic lupus patient who served as a control. Results are shown as the percentage of T lymphocytes with cytokine synthesis

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFy</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE</td>
<td>Basal PGE</td>
<td>Basal PGE</td>
</tr>
<tr>
<td>Control</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Patient</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

IL2, interleukin; INFy, interferon y. Whole blood was incubated with or without PGE, 10 ng/ml, for six hours in the presence of Brefeldin-A. Cells were stained with FITC-CD3 and, after erythrocyte ly sis and permeabilisation, with the phycoerythrin conjugated anti-cytokines. Samples were analysed by flow cytometry.
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblast activity, is inversely correlated with the extent of joint inflammation. 1 Synovial and serum osteocalcin correlate positively. 2 In ankylosing spondylitis (AS) the serum concentration of osteocalcin has been reported to be low 3 or normal. 4 Cross sectional studies have shown no significant correlation between osteocalcin serum concentration and erythrocyte sedimentation rate (ESR) or C reactive protein. 5

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 sensitive and specific. For this reason changes in ESR, which is probably still the best marker of inflammation in AS. 6

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female) the age range according to the manufacturer was 7.5–31.5 ng/ml in men, 7.3–31.7 ng/ml in women. Results are given as median (25th, 75th) percentile. The Mann-Whitney sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 18 (8, 28) mm/h, serum osteocalcin 25 (20.5, 52.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/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/h) and changes in osteocalcin (−0.3 to −6.57 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.

Takayasu arteritis

Takayasu arteritis is a chronic inflammatory vasculitis that occurs primarily in young women. It occurs world wide, with greatest prevalence in Asian people. It mainly affects the aorta and its major branches. The Centres for Disease Control and Prevention have broadly defined idiopathic CD4+ T lymphocytopenia as a reproducible depletion of CD4 lymphocytes below 0.3 x10^9/l in the absence of HIV infection or other known causes of immunodeficiency. We report a case of Takayasu arteritis with low CD4+ T lymphopenia without evidence of HIV infection in a boy from Turkey.

A 9-year-old boy was admitted with a history of dyspnoea, malaise, and cough for four months. Before admission the patient had been prescribed treatment for pneumonia. He had no history of recurrent infection until four months before admission. There was no parental consanguinity or any immunocompromised person in his family. Physical examination showed a temperature of 36°C, pulse rate of 140 beats/min, respiratory rate of 30/min, and a blood pressure of 110/70 mm Hg. His weight and height were below the fifth centile. He had a gallop rhythm, grade 3/6 pansystolic murmur at the 4th–5th left intercostal space and hepatomegaly. A chest x ray examination showed cardiomegaly and pulmonary oedema. The following laboratory values were obtained: haemoglobin 113 g/l packed cell volume 0.35, leucocyte count 8.3 x10^9/l, platelet count 371 x10^9/l, erythrocyte sedimentation rate 71 mm/1st h. Other test findings, including serum electrolytes, blood urea nitrogen, and creatinine, were all normal. Echocardiography showed a dilated cardiomyopathy associated with severe mitral and aortic insufficiency. The patient was treated for heart failure with inotropic agents and furosemide (frusemide) and improved greatly.

At the fourth month of follow up a physical examination showed hypertension and decreased left radial and brachial pulses. A systolic blood pressure difference greater than 10 mm Hg between both arms appeared (right arm, 140/100 mm Hg; left arm, 110/70 mm Hg). Laboratory findings showed increased blood urea nitrogen and creatinine levels. Urine analyses disclosed microscopic haematuria and mild proteinuria. Antinuclear antibodies were positive (1:20). Protein electrophoresis showed a decreased serum albumin level, hypergammaglobulinaemia, and increased IgG, globulin. Serum C3 and C4 levels were normal. HLA-B27 was negative. Table 1 shows the immunological findings of this patient. A lymphocyte proliferation test was not carried out on the patient. Enzyme linked immunosorbent assay (ELISA) and polymerase chain reaction tests for HIV-1 and HIV-2 were repeatedly negative, but we did not look for HTLV-1 and HTLV-2. Echocardiography showed dilatation of the thoracic aorta and stenosis of the left subclavian artery. Magnetic resonance imaging showed dilatation of the renal arteries. The patient underwent catheterisation and aortography. Angiographic examination showed narrowing of the left subclavian artery, dilatation of the thoracic aorta, and occlusion of the superior mesenteric and renal arteries. Moreover, the patient’s left kidney could not be visualised. Takayasu arteritis was diagnosed and the patient received prednisone treatment (2 mg/kg/day), but he died in the initial steroid treatment period owing to severe cardiac failure. Takayasu arteritis may be the third most common form of childhood vasculitis after...
Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-aorta antibodies in the serum of some patients with this condition have suggested an immunological cause and, possibly, an autoimmune process.

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

All patients with idiopathic CD4+ T lymphophyenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4 x 10^9/l, to determine the natural history of their infections and lymphophyenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking.


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 diplopa. 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 bacterial infections, and antibodies against Borrelia burgdorferi were absent. Autoantibodies (antinuclear antibodies, anti-DNA, antistreptolysin, antinuclear antibodies, anti-DNA antibodies and anti-DNA antibodies were undetectable. Other markers that are considered measures of disease activity in juvenile idiopathic myopathies were evaluated: factor VIII related antigen levels were raised, while neopterin levels and the number of circulating B lymphocytes (CD19 positive cells) were normal. Electrocardiography and two dimensional echocardiography excluded a concurrent myocarditis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (ScI), Crohn's disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extraocular muscles 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, ScI, giant cell myocarditis, and Crohn's disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease; ocular myopathies, such as mitocondrial disorders and ocular dystrophies; and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinus thrombosis are also included in the differential diagnosis.

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

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

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References


Sciatica or spinal lymphoma

The involvement of the central nervous system and vertebrae by low grade non-Hodgkin’s lymphoma is rare.\(^1\) In a previous “lesson of the month” in this journal, it was implied that there is always a bad prognosis for patients with spinal lymphoma; however, milder cases may also occur. A 71 year old man presented to us in January 2000 with a three month history of severe low back pain affecting mainly the left lumbar area and buttock, radiating to the outer aspect of the left thigh and calf. He did not have bladder symptoms or history of recent falls. On examination, he looked well; there was no lymphadenopathy. He had restricted back movement with tenderness of lower lumbar spinal processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and co-ordination. 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 phenobarbitalone. In 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hypersplenism. Splenectomy was performed in 1994, his blood count returned to normal, and repeated full blood counts were stable. In 1995 the patient had a fall and severe back pain. A magnetic resonance imaging (MRI) scan showed collapse of T7 and wedging of T4, with evidence of osteoporosis but no infiltration. Treatment was started with etidronate and calcium.

Investigations showed normal serum biochemistry apart from a mild increase of alkaline phosphatase, which was 242 IU/l (normal 60–220). The total white cell count was 24.7×10^9/l, differential count showed neutrophils 3.5×10^9/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 lumberosac spine x ray examination showed biconcave L3 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 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\(^2\) 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 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 ovary. A cholecystectomy and right anexectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was 4.89×10⁹/l with 22% eosinophils, erythrocyte sedimentation rate (ESR) 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/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and haem and hyalino 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 1.05×10⁶/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovariun histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polypsis.

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, with initial clinical improvement. However, cyclophosphamide 100 mg/day were started, owing to right upper quadrant pain. 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 torpid, and sometimes only diagnosed at necropsy. Abdominal ultrasonography should be included in the routine screening of patients with CSS.

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

The ascitic fluid, rich in eosinophils, the eosinophil infiltration of major omentum samples and the clinical evolution suggest that the peritoneal involvement was due to the CSS, an extremely rare complication of 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.

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

References
22nd European Workshop for Rheumatology Research
28 Feb–3 Mar 2002; Leiden, The Netherlands
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5th European Conference on Systemic Lupus Erythematosus
26–30 May 2002; Athens, Greece
Chairman Professor HM Moutsopoulos
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Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
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29th Scandinavian Congress of Rheumatology
15–18 Aug 2002; Tromso, Norway
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Translational Research in Autoimmunity
21–22 Sep 2002; Pavia, Italy
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Email: tra@e20pr.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
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10th International Congress on Antiphospholipid Antibodies
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Deadline for abstracts 1 April 2002
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7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases
14–17 Oct 2002; Nashville, Tennessee, USA
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66th American College of Rheumatology AGM
25–29 Oct 2002; New Orleans, USA
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Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis
7–9 November 2002; Barcelona, Spain
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Certifying Examination in Pediatric Rheumatology
18 Nov 2002
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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