**MATTERS ARISING**

### Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled “Antiphospholipid antibodies and RA: presence of β2-glycoprotein I independent aCL” by Bonnet et al published in the *Annals in March 2001*. We believe that the letter needs additional clarification owing to inconsistencies in the terminology, methodology of antiphospholipid antibody (aPL) detection, and determination of positive values.

The use of the term “anticardiolipin antibodies” was somewhat misleading. The term was introduced and abbreviated as “aCL”, a group of antibodies detected in many conditions, but the β2-glycoprotein 1 (β2GP1) dependance of the aCL was not defined, even though the authors focused on β2GP1 independent aCL. It is generally agreed that the term aCL, if not stated otherwise, defines the antibodies detected by the classical aCL enzyme-linked immunosorbent assay (ELISA). —that is, both β2GP1 dependent and β2GP1 independent antibodies.

There were some potential methodological errors in determining β2GP1 independent aCL. It was shown that antibodies against β2GP1 (anti-β2GP1) from patients with the antiphospholipid syndrome (APS) have the ability to bind β2GP1 in complexes with cardiolipin only if the β2GP1 concentration in solution is high enough. The threshold concentration of β2GP1 was found to be just about 2 µg/ml, because no binding of anti-β2GP1 was seen when serum samples were diluted 1:200 or more. As the physiological concentration of β2GP1 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 β2GP1, the statement that antibodies detected by this method are exclusively β2GP1 independent is unjustified, as the sera containing high titres of anti-β2GP1 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 β2GP1 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, β2GP1 dependent aCL. β2GP1 independent aCL were not defined in those standards and they were not meant as standards for β2GP1 independent assays.

The interpretation of anti-β2GP1 ELISA as a method to detect β2GP1 dependent aCL may not be valid in all cases. It was shown that not all anti-β2GP1 binding β2GP1 adsorbed on polystyrene high binding plates also recognise β2GP1 associated with cardiolipin. We reported this binding pattern for anti-β2GP1 in children with atopic dermatitis, and the same was shown also for some patients with autoimmune diseases, including APS.

The method for purification of β2GP1 was not described. Because the authors focused on patients with rheumatoid arthritis (RA), it should be ensured that immunoglobulins were specifically removed from the β2GP1 preparation. If this purification step was not carried out, traces of immunoglobulins in the β2GP1 preparation might have yielded positive results for sera containing high titres of rheumatoid factor (RF). In fact, all sera containing IgM anti-β2GP1 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 β2GP1 independent aCL and for anti-β2GP1. We recently compared the sensitivity of anti-β2GP1 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-β2GP1, β2GP1 dependent aCL, and β2GP1 independent aCL. The assays were calibrated with β2GP1 dependent monoclonal aCL (IgG and IgM anti-β2GP1 ELISA and β2GP1 dependent aCL ELISA) and positive in-house standards (all IgA assays and β2GP1 independent aCL). The cut off values for anti-β2GP1 were set as described by calculating the mean + 2 SDs of logarithms of absorbance values for NHS and the 95th centile value of 32 NHS for both β2GP1 dependent and β2GP1 independent aCL. For the anti-β2GP1 determination, we used affinity purified β2GP1 adsorbed on Costar high binding plates as previously described. The β2GP1 preparation did not contain any immunoglobulin G or IgM. β2GP1 independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for β2GP1 dependent aCL on the same plate by adding β2GP1 in parallel duplicate wells. The final concentration of β2GP1 was 10 µg/ml. This experimental design enabled direct comparison of binding to cardiolipin coated wells in the presence and absence of β2GP1. For the final determination of β2GP1 dependent binding, the values obtained in wells without β2GP1 were subtracted from the values measured in wells with added β2GP1. 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-β2GP1, β2GP1 dependent aCL, and β2GP1 independent aCL was higher in patients with RA than in controls, but the difference was significant only for anti-β2GP1. There were no differences in the frequency of

| Table 1: Frequency of anti-β2GP1, β2GP1 dependent aCL, and β2GP1 independent aCL in patients with rheumatoid arthritis (positive or negative for RF) and normal controls |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-β2GP1** | **β2GP1 dependent aCL** | **β2GP1 independent aCL** |
| | IgG | IgM | IgA | Any Ig | IgG | IgM | IgA | Any Ig | IgG | IgM | IgA | Any Ig |
| No of positive samples: | No | % | No | % | No | % | No | % | No | % | No | % |
| NHS (n=53) | 3 6 2 1 | 2 1 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 |
| RA (n=53) | 3 6 1 1 | 2 1 1 1 | 2 1 1 1 | 2 1 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 |
| RA-RF (n=36) | 3 6 1 1 | 2 1 1 1 | 2 1 1 1 | 2 1 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 | 2 2 1 1 |
| RA-RF (n=17) | 1 2 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 | 3 3 1 1 |

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. 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 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 has not been fully clarified. It seems the presence of β2GP1 independent aCL do not confer an increased risk for APS in RA.

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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 despaired of answering this question definitively owing to the difficulty in recruiting subjects. It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of complications.

Despite this important finding, we believe that the results of this study should be regarded with some reservation: continuation of methotrexate throughout the perioperative period should be accompanied by significant caution. The elderly and those with renal impairment are at increased risk of methotrexate-related pancytopenia. Indeed, in a community-based, observational study of methotrexate use in 460 patients we found the number of normal subjects (blood donors) as previously described. In this study, 50 serum samples, provided by consenting healthy donors, were tested as controls.

Cut off values were determined as the mean and two standard deviations of the arbitrary units obtained by reference to positive and negative internal standards. For every serum, we defined the corrected optical density (OD) (that is, the mean OD obtained in three coated wells minus the OD corresponding to non-specific binding of each serum, obtained in three uncoated wells). The cut off values defined for anti-β2GP1 and anti-cardiolipin ELISA were 20 units in both tests. The standards for the anti-β2GP1 test were provided by positive controls from patients with APS and were used according to previous studies.

In contrast with the report of Ambrozic et al, we did not find raised levels of aCL or anti-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 related with a differing sensitivity and specificity of the methods between the two laboratories.

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References

periperoic 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 Wighton 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 alter disease control in the vast majority of patients, although after four weeks without treatment, most will have a flare of the disease.5

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

It is rare for coeliac disease to present only with symptoms of osteomalacia, without the classic symptoms of diarrhoea, steatorrhoea, and abdominal discomfort.6

A 22 year old woman presented with 18 months of a waddling gait disturbance, hip and back pain 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 B thalassaemia minor and iron deficiency. Other investigations disclosed a raised alkaline phosphate of 1375 U/l (normal 30–120 U/l), reduced red blood cell folate level of 290 nmol/l (>300 nmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.0 mmol/l (0.8–1.4 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, antiendomyosal 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 150 mg daily, and repeat gastroscopy and duodenal biopsy within two months. 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 1965,7 there have been several case reports of coeliac disease presenting with bone pain, proximal myopathy, radiographic findings of pseudostructures and Looser’s zones, or secondary hyperparathyroidism evident on bone scan.8 Most patients were middle aged and responded within six months to treatment with a gluten-free diet, supplemental calcium, and vitamin D, and in some cases with the addition of bisphosphonates.9 A recent case finding study of coeliac disease showed that many patients in fact present with non-gastrointestinal symptoms, of which anaemia is the most common.

Hypocalcaemia in coeliac disease is caused by reduced gut absorption of calcium as a consequence of reduced levels of the fat soluble vitamin D. It is also due to reduced absorptive surface area, secondary hyperparathyroidism, and calcium lost in the stools by binding to unabsorbed fatty acids to form insoluble calcium soaps.10

Secondary hyperparathyroidism can develop, but it did in this case, causing increased bone turnover. Low bone mineral density is probably due to a combination of hypocalcaemia, impaired bone mineralisation, and reduced exercise because of skeletal pain and proximal weakness.11

Early diagnosis of coeliac disease is important because untreated patients have an increased risk of gastrointestinal lymphomas. Useful screening blood tests include determination of antigliadin and antienthymosial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.12 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.

Treatment with a gluten-free diet with subsequent villous restitution on repeat biopsy has been associated with rapid gains and even normalisation of bone mineral density; the greater the degree of osteopenia, the more rapid the gain.13 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.14

Introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.15

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 hormone replacement therapy including vitamin D may lead to rapid and effective recovery.8

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

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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/h.

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

Thirty nine patients (31 women) with RA had a mean (SD) age of 36.2 (8.3) years (range 18–52) and mean disease duration of 35.8 (36.6) months (range 6–186). Twenty patients had inactive and 19 patients active disease, respectively. Twenty two healthy controls (14 women), well matched for age (mean age 34.2 (6.2) years, range 20–56) with the two patient groups, were studied at the same time. Both patients and controls were of middle socioeconomic status. Table 1 shows the plasma and PBMC levels of Zn and Cu.

Our results are in agreement with earlier studies which showed that plasma Zn levels are significantly lower and plasma Cu levels significantly higher in patients with active RA. Additionally, it has been 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 copper concentration may not be indicative of overall deficiency. Possibly, also, PBMCs may be an additional site to which Zn is moved during inflammatory states. The average disease duration of patients with active disease was more than 54 months. In such a long process it is unclear whether chronic cytokine release, as is seen in RA, causes a shift of Zn from one compartment to another or if there is a true Zn depletion. Significantly, there was no correlation between age or duration of disease and plasma or PBMC levels of Zn.

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

The effect of concomitant drugs must be considered. The number of patients receiving non-steroidal anti-inflammatory 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.

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References

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 gammapathy 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 serum viscosity; antinuclear antibodies could not be detected and neither could rheumatoid factor. Complement components (C1q, C2, C4, C3) showed normal levels. In our patients we were able to show that paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the serum viscosity; antinuclear antibodies could not be detected and neither could rheumatoid factor. Complement components (C1q, C2, C4, C3) showed normal levels. In our patients we were able to show that paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the serum viscosity; antinuclear antibodies could not be detected and neither could rheumatoid factor. Complement components (C1q, C2, C4, C3) showed normal levels. In our patients we were able to show that paraproteins can be precipitated by lowering the temperature below 37°C. In this way they form an essential part of the serum viscosity; antinuclear antibodies could not be detected and neither could rheumatoid factor. Complement components (C1q, C2, C4, C3) showed normal levels.

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 right hand became necrotic. Angiography of his upper part of the third finger of his left hand showed normal vessels. Immune electronphoresis showed the presence of 8 g/l of an M component (IgGκ). An assay for the detection of cryoglobulinaemia was positive. Laboratory examination showed very low levels of the complement component C1q (6 mg/ml) and prednisone (60 mg/day), which improved the necrosis of her legs. The necrosis of her right leg disappeared and on the left foot the necrosis began to demarcate to the upper part of her foot. While waiting for the complete demarcation so that an amputation could be planned, she developed a sepsis and died.

Few patients with essential cryoglobulinaemia type 1 have been reported. Until now a defined clinical syndrome could never be associated with classification of the cryoglobulins. Overall Raynaud’s phenomenon, and necrosis of the skin has been described as in our three patients. None of our three patients showed abnormalities on angiographical 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 monochonal immunoglobulin. When the serum concentration of the cryoglobulins was reduced, the disease symptoms in our patients improved. These cases suggest that a paraprotein found in patients with a rheumatic syndrome is not only indicative of a developing malignancy or other disease but may also be interpreted as a causative agent. We conclude that paraproteins seen in rheumatic syndromes have a role in the pathogenesis and should be treated when serious sympoms are present.

References


Cryoglobulinemia as presenting manifestation of infective endocarditis

Seromunnomological alterations, including antibodies and/or cryoglobulins, are commonly seen in infective endocarditis (IE). Thus specific autoimmune diseases, such as cryoglobulinemia varicella (CV) associated with IE have seldom been described. CV is related to the vascular deposition of circulating immune complexes, mainly cryoglobulins, and complement components; in 70–90% of patients with CV a triggering role of hepatitis C virus (HCV) has been suggested. We report the case of two patients who showed a typical CV with severe neurological involvement as the presenting manifestation of underlying IE.

Case 1

In November 1994 a 63 year old woman presented with fever, purpura, paraesthesias, and pseudoatotic gait. Her past clinical history was unremarkable except for a prostatic implant of the left hip four years previously. Table 1 shows the main clinicoserological features. Repeated blood cultures were negative. Neurological examination showed abnormal tactile sensation on the arms and legs; mild ideomotor slowing down; shaky movements; and unsteady gait. An electrophysiological study recorded a moderate sensorimotor peripheral neuropathy, while chest x-ray examination, abdominal echography, and ecocardiography were normal. Cutaneous purpura biopsy disclosed a leucocytoclastic vasculitis. Truncocerephalic magnetic resonance imaging showed a weighted high signal intensity, punctiform lesions at the white matter consistent with brain vasculitis. Thus a central and peripheral nervousopathy complicating CV was established, and prednisone (50 mg) combined with cyclophosphamide (100 mg) was given daily. However, the patient's clinical status progressively worsened and, finally, she died owing to cardiorespiratory failure 12 months after a year of treatment. Necropsy disclosed coarse endocardial vegetations on the left sides valves infected by Vangella.

Case 2

In January 1999 a 75 year old woman with no risk factors for infections presented with fever, purpura, and acroparaesthesias. Table 1 shows the main clinical and laboratory features suggestive of CV. Prednisone (25 mg/day) was started, with a rapid clinical improvement. One month later, she had an exacerbation of purpura, arthralgias, acroparaesthesias, and impairment of distal muscle strength. An electrophysiological study confirmed a sensorimotor peripheral neuropathy. Thus a higher steroid dose (50 mg/day) was given. A week later fever persisted and the patient complained of precardial pain and cardiac murmurs were found. A chest x-ray examination and transaxecophageal echochography detected cardiomegaly and endocardial vegetations on the tricuspid valve; in addition, Staphylococcus aureus infection was shown by repeated blood cultures. Despite appropriate antibiotic treatment, the patient died one month later because of severe cardiorespiratory failure.

Discussion

Our two patients show some interesting peculiarities: the unusual presentation of IE
as CV with severe neurological involvement; and the difficulty of making a timely diagnosis of IE by routine investigations. In both cases, the predominantly CV symptoms were associated with fever, edema, headache, and pain, accompanied by hypotension and a positive cardiac auscultation. In patient 1, the lack of timely recognition and suitable treatment recommended by the treating physician significantly increased the patient’s risk of complications. In patient 2, the delayed diagnosis of IE responsible for the CV symptoms was likely due to the patient’s underlying immunosuppressive condition.

Moreover, the CV seen in our two patients had a distinct pattern; these patients presented with neurological involvement, mostly due to microangiopathy, and shock. Of interest, the presence of fever was more common in patients with CV and shock than in those with CV alone. This is in line with the hypothesis that fever may be associated with a more severe form of CV, leading to a higher mortality rate.

Furthermore, ANCA positivity was strongly associated with CV in our study, and ANCA positivity was present in all patients with CV and shock. ANCA positivity is a marker of vasculitis, and it is associated with a higher risk of complications and mortality. In our study, ANCA positivity was strongly related to the presence of shock, and it was present in all patients with CV and shock.

Several drugs have been associated with ANCA positivity, including hydralazine, penicillamine, allopurinol, and propylthiouracil. Propylthiouracil is a drug used to treat hyperthyroidism, and it has been associated with ANCA positivity in a number of studies. Hydralazine is a drug used to treat hypertension, and it has been associated with ANCA positivity in a number of studies. Penicillamine is a drug used to treat rheumatoid arthritis, and it has been associated with ANCA positivity in a number of studies. Allopurinol is a drug used to treat gout, and it has been associated with ANCA positivity in a number of studies.

Although propylthiouracil is often implicated in the induction of ANCA positive vasculitis, other antithyroid drugs, such as carbimazole and thioureas, have also 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 CV and shock. The study included 35 serum samples from 35 patients with CV and shock. ANCA positivity was detected in 21 (60%) of the patients, and it was associated with a more severe form of CV and a higher mortality rate. ANCA positivity was strongly related to the presence of shock, and it was present in all patients with CV and shock.

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

| Patient | Age (years) | Disease duration (weeks) | Purpura | Weakness | Arthritis | Hepatopathy | Nephropathy | Neurological involvement | Cardiac symptoms | ESR (mm/1st h) | CRP (normal <5 mg/l) | WBC (normal 5–10 × 10⁹/l) | γ-Globulinaemia (g/l) | RF (normal <20 IU/ml) | Anti-MPO | Anti-MPO-ANCA | Anti-PR3-ANCA | Hepatitis virus markers* |
|---------|-------------|--------------------------|---------|---------|-----------|-------------|-------------|--------------------------|----------------|--------------|---------------------|------------------------|-----------------------|----------------|----------------|----------------|------------------------|
| Patient 1 | 63          | 7                        | Absent  | Severe  | Absent    | Absent      | Absent      | Peripheral-central Peripher | Absent          | 83           | 1490                | 89 000                 | 19.5                   | 575                  | Negative | -              | -              | Negative               |
| Patient 2 | 77          | 9                        | Absent  | Mild-moderate | Absent    | Absent      | Absent      | Peripheral | Absent          | 73           | 77          | 53                  | 89 000                 | 21.3                   | 157                  | Negative | Negative       | Negative       | Negative               |

*HbsAg, anti-HBs, anti-HbcIgM, anti-Hbc, anti-HCV by ELISA and RIBA; anti-EBV IgM, anti-HIV.

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 and shock. The study included 35 serum samples from 35 patients with CV and shock. ANCA positivity was detected in 21 (60%) of the patients, and it was associated with a more severe form of CV and a higher mortality rate. ANCA positivity was strongly related to the presence of shock, and it was present in all patients with CV and shock.

Our results are very similar to those of Alettra et al, who reported ANCA positivity by IIF in 6/21 (29%) patients with CV and shock. The IIF staining pattern was ANCA in all cases. ANCA positivity was detected only in one (5%) of the patients. In our study ANCA were detected in 21 (60%) serum samples. The ANCA staining patterns were more heterogeneous, but the ELISA results were similar.

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Human MPO and human thyroid peroxidase (TPO) share global similarities which indicate that MPO and TPO are members of the same gene family. Therefore, it seems conceivable that MPO autoantibodies may cross react with TPO. Findings suggesting such a relationship were reported by Haapala et al., who found antibodies against both TPO and MPO in 19 patients, three with vasculitis and 16 with thyroid disorders.1

There is a need to determine the auto-antigenic 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 (thiazole or propylthiouracil) or to the disease itself.

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References

Lupus relapse after prostaglandin E administration: activation of a cytokine cascade?
A variety of abnormalities in cytokine production occur in human and murine lupus, but their specific role in lupus pathogenesis is unknown. Recent in vitro studies emphasise the role of prosta glandins in the cytokine induction and modulation of the humoral immune response.9–11 We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E (PGE) administration, which to our knowledge has not been previously reported.

A 25 year old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud’s phenomenon. During five years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy proven diffuse proliferative lupus glomerulonephritis (WHO class IV). A physical examination showed only painful, violaceous, and atrophic finger pads with no signs of systemic inflammatory disease. The chest X ray films were normal and laboratory investigations showed antinuclear antibodies (ANA; titre 1/160) and hypocomplementaemia (C3 0.6 g/l, C4 0.1 g/l), with normal liver, renal, and haematological parameters. Treatment with 40 mg/12 h IV PGE, was started. On the sixth day of treatment the patient began to have chest pain, fever, dyspnoea, and pericardial friction rub. The laboratory showed anaemia, modest thrombocytopenia, and ANA 1/320, with no changes in the rest of the biochemical serum parameters. Echocardiography and chest X ray examination showed moderate pericardial and bilateral pleural effusions. PGE, was withdrawn and a dose of intravenous, 60 mg/day, was started with prompt improvement in the symptoms.

We investigated the possibility that PGE mediated cytokine production might be the cause of the relapse of SLE in this patient. Intracellular expression of cytokines in the patient’s T lymphocytes after specific PGE stimulation (table 1).

Table 1

<table>
<thead>
<tr>
<th>IL2</th>
<th>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal PGE</td>
<td>Basal PGE</td>
<td>Basal PGE</td>
</tr>
<tr>
<td>Control</td>
<td>Patient</td>
<td>Patient</td>
</tr>
<tr>
<td>1.2</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>0.8</td>
<td>0.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

IL, interleukin; INFγ, interferon γ.
Whole blood was incubated with or without PGE, 10 ng/ml, for six hours in the presence of Brefeldin-A. Cells were stained with FITC-anti-CD3 and, after erythrocyte lysis and permeabilisation, with the phycoerythrin conjugated anticytokines. 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 low3 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 best marker of inflammation in AS.6

In 89 patients with ankylosing spondylitis (modified New York criteria; 75 male, 14 female; age 43 (11) years; disease duration 14 (9) years) venous blood was taken at the start and the end of a three week rehabilitation (9) years) venous blood was taken at the start and the end of a three week rehabilitation (9) years). The serum osteocalcin concentration was within the normal range in 18 (8, 28) mm/1st h, serum osteocalcin 25 4–7 ng/ml (modified New York criteria; 75 male, 14 female; age 43 (11) years; disease duration 14 (9) years). The serum osteocalcin concentration was within the normal range in 18 (8, 28) mm/1st h, serum osteocalcin 25 4–7 ng/ml. Serum osteocalcin determination for assessment 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 his 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 8.3×10³/l, platelet count 371×10³/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 (g/l) 23.3 (8.4–19.4) and IgM (mg/l) 531 (240–390) levels. HaLA-B52 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 disclosed dilatation of the thoracic aorta and stenosis of the left subclavian artery. Magnetic resonance imaging showed dilatation and irregular contour of the arch, occlusion of the descending aorta, and narrowing of the abdominal aorta (fig 1). The patient underwent cardiac 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

### References


### Takayasu arteritis

Takayasu arteritis is a chronic inflammatory vasculitis that occurs primarily in young women. It affects the aorta and its major branches.1 The disease is characterised by the destruction of the arterial wall, with severe inflammatory reaction leading to the narrowing or occlusion of the affected vessels. The condition affects the thoracic and abdominal aorta, and is more common in women of Asian origin. The aorta and its branches are affected, with the thoracic aorta being the most commonly involved. The disease is typically associated with systemic inflammatory markers, such as elevated C-reactive protein and erythrocyte sedimentation rate.

### Table 1

<table>
<thead>
<tr>
<th>Immunological data of the patient</th>
<th>Values</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count (×10⁹/l)</td>
<td>1.5</td>
<td>&gt;2</td>
<td></td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>23.3</td>
<td>(8–19.4)</td>
<td></td>
</tr>
<tr>
<td>IgM (mg/l)</td>
<td>6290</td>
<td>(620–3980)</td>
<td></td>
</tr>
<tr>
<td>α2-globulin (mg/l)</td>
<td>531</td>
<td>(240–390)</td>
<td></td>
</tr>
<tr>
<td>CD3 (×10⁹/l)</td>
<td>1.2</td>
<td>0.7–4.2</td>
<td></td>
</tr>
<tr>
<td>CD4 (×10⁹/l)</td>
<td>2.0</td>
<td>0.3–2.0</td>
<td></td>
</tr>
<tr>
<td>CD8 (×10⁹/l)</td>
<td>1.0</td>
<td>0.3–1.8</td>
<td></td>
</tr>
<tr>
<td>CD19 (×10⁹/l)</td>
<td>0.3</td>
<td>0.3–1.2</td>
<td></td>
</tr>
<tr>
<td>CD3–CD16+CD56 (×10⁹/l)</td>
<td>0.2</td>
<td>0.1–0.9</td>
<td></td>
</tr>
</tbody>
</table>

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Hench-Schönlein purpura and Kawasaki disease. Raised immunoglobulin levels and the finding of anti-ana 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 common 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 lymphocytopenia need to be observed prospectively and tested after their opportunistic infections, or after their first CD4+ cell count less than 0.4x10^9/L, to determine the natural history of their infections and lymphocytopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking. Further investigations of cases of idiopathic CD4+ T lymphocytopenia—on analysis of five patients with unexplained opportunistic infections. N Engl J Med 1992;328:328-329.


Recurrent orbital pain and diplopia in a 12 year old boy

A previously healthy 12 year old boy was referred to our unit in May 2000, with a history of persistent ocular pain and recurrent diplopia. The first relapse 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 myasthenia gravis, prescribed naproxen (30 mg/kg/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 myocarditis, and Crohn’s disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease, ocular myopathies, such as mitochondrial disorders and ocular dystrophies, and orbital pseudotumours. Cellulitis, neoplasms, arteriovenous malformations, and cavernous sinus thrombosis are also included in the differential diagnosis.

Orbital myositis implies orbital inflammation confined to one or more of the extraocular muscles. This case report suggests that low CD4+ lymphopenia may cause dysgammaglobulinaemia and autoimmunity syndromes such as Takayasu arteritis.

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References


Hodgkin’s lymphoma is rare. System and vertebrae by low grade non-
Sciatica or spinal lymphoma

cyclosporin have been used with success.

In our patient, cyclosporin was successful as a steroid sparing agent, because a rapid recur-
rence 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 paresis in the differential diagnosis.

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References


Sciatica or spinal lymphoma

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

A 71 year old man presented to us in January 2000 with a three month history of severe low back pain affecting mainly the left lumbar area and buttock, radiating to the outer aspect of the left thigh and calf. He did not have bladder symptoms or history of recent falls.

On examination, he looked well; there was no lymphadenopathy. He had restricted back movement with tenderness of lower lumbar 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 1995 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hyperplenism. 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 bio-
chemistry 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 sedi-
mentation 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 splenec-
tomy, but no enlarged lymph nodes were detected. A bone isotopic scan showed in-
creased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenera-
tive 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, anal-
gesics, and physiotherapy. His haematologist started treatment of the patient with chlor-
ambucil 10 mg/day for 10 days to be repeated every three weeks, these cycles to be con-
tinued 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 presenta-
tion with low back pain appeared to be a typi-
cal 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 presenta-
tion 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 syn-
drome (CSS), bowel perforations, cholecystitis, eosinophilic peritonitis, and oophoritis are very unusual and normally resolve after immuno-

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suppressive treatment. We report the case of a patient with CSS with these complications, which was fatal despite proper treatment.

A 64 year old woman with a 13 year history of urticaria, recurrent rhinitis, and asthma was admitted for abdominal pain. An increas-
ing 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 ab-

nal ultrasound performed during an asthma exacerbation when she had no abdominal pain disclosed a thick-walled gall bladder with no echogenic contents. An excited nasal polyp showed polypoid hyperplasia with many eosinophils.
underwent a second laparotomy after three the abdominal pain recurred and the patient with initial clinical improvement. However, the leucocyte count was 1×10⁹/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed a calculeous 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, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal <80), and total IgE 769 IU/ml (normal <100), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antineutrophil cytoplasmic antibody values were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells/low power field, 3–5 leucocytes, and hyaline and hyaline granular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid was seroserosinous with a protein concentration of 55 g/l, a leucocyte count of 1.05×10⁹/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovarian histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyposis.

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

Abdominal pain is reported in up to 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 ovariurn involvement.

The ascitic fluid, rich in eosinophils, the eosinophilic infiltration of major omentum samples and the clinical evolution suggest that the peritoneal involvement was due to the CSS, an extremely rare complication of this disease. Eosinophilic peritonitis was suggested by Lanham owing to serosal involve ment 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 arthritis is found (haematoxylin and eosin ×25, and left lower quadrant ×200).

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 a calculeous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right anexectomy were performed.

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28 Feb–3 Mar 2002; Leiden, The Netherlands
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Email: F.C.Breedveld@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.
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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
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Fax: +44 208569 9555
Email: tony@c2q.co.uk or p.brooks@mailbox.uq.edu.au

British Society for Rheumatology XIXth AGM
23–26 Apr 2002; Brighton, UK
Contact: BSR, 41 Eagle Street, London WC1R 4TL, UK
Website: www.rheumatology.org.uk

4th EULAR Sonography Course
25–28 April 2002; Madrid, Spain
The course is entitled “Practical use of musculoskeletal ultrasonography”
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10th International Vasculitis and ANCA Workshop
25–28 Apr 2002; Cleveland, Ohio, USA
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Website for registration and abstract submission: www.clevelandclinicmeded.com/courses/Vasculitis2002.asp

International Congress: New Trends in Osteoarthritis
9–11 May 2002; Milan, Italy
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Fax: +39 02 65 71 270
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IOF World Congress on Osteoporosis
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Email: info@ioflyon.org
Website: www.osteofound.org

5th European Conference on Systemic Lupus Erythematosus
26–30 May 2002; Athens, Greece
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Secretariat: Amphi fhion Congress Organising Bureau
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Website: congress@amphi fhion.gr

Annual European Congress of Rheumatology
12–15 June 2002; Stockholm, Sweden
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Fax: +41 1 383 9810
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10th International Congress on Behcet’s Disease
27–29 June 2002; Berlin, Germany
Under the auspices of the International Society for Behcet’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, Fabeckstraße 60–62, 14195 Berlin, Germany
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29th Scandinavian Congress of Rheumatology
15–18 Aug 2002; Tromso, Norway
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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
Fax: +39 02 638 925
Email: tra@e20pr.com
Website: www.e20pr.com
Congress website: www.medicine.ucsd.edu/albani/2001meeting

OsteoArthritis Research Society International (OARSI) World Congress
29–25 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 Kones International, PO Box 50006, Tel Aviv 61500, Israel
Tel: 972 3 5140018/9
Fax: 972 3 5140077 or 972 3 5172484
Email:aps@kones.com
Website: www.kones.com/aps

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

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

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

Certifying Examination in Pediatric Rheumatology
18 Nov 2002
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA
Tel: 919 929 0461
Fax: 919 929 0460
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

www.annrheumdis.com
Antiphospholipid antibodies and rheumatoid arthritis

A Ambroziec, B Bozic, M Hojnik, T Kveder and B Rozman

Ann Rheum Dis 2002 61: 85-86
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