PostScript

MATTERS ARISING

Antiphospholipid antibodies and rheumatoid arthritis

We read with interest the letter entitled “Antiphospholipid antibodies and RA: presence of β2GP1 independent aCL” by Bonnet et al published in the Annals in March 2001.1 We believe that the letter needs additional clarification owing to inconsistencies in the terminology, methodology of antiphospholipid antibody (aPL) detection, and determination of positive values.

The use of the term “anticardiolipin antibodies” was somewhat misleading. The term was introduced and abbreviated as “aCL”, a group of antibodies detected in many conditions, but the β2 glycoprotein I (β2GP1) dependence 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).2— 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.3 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,4 the units should be abbreviated as GPL (for IgG) and MPL (for IgM) as previously defined.5 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 dependent aCL 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,6 and the same was shown also for some patients with autoimmune diseases, including APS.7

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.8 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 cut off values for anti-β2GP1 were set as described9 by calculating the mean + 2 SD 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.10 The β2GP1 preparation did not contain any immunoglobulins. β2GP1 independent aCL were tested as described in the letter, but the sera were diluted 1:200. Serum samples were tested simultaneously for anti-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...
any type of antibodies between the RF positive and negative patients. One patient (a male, 66 years old) had a history of deep venous thrombosis and pulmonary embolism together with positive anti-β2-GP1 and β2-GP1 dependent aCL of IgA isotype. Interestingly, 9/11 RA sera which showed binding to β2-GP1 adsorbed on a high binding plate did not recognise β2-GP1 associated with cardiolipin, as already reported. In contrast, 9/9 RA sera binding β2-GP1 complexed with cardiolipin did not recognise β2-GP1 adsorbed on the surface of high binding plates. This phenomenon probably reflects the heterogeneous nature of anti-β2-GP1 in RA, which may differ in fine specificity between anti-β2-GP1 in APS.

The sera from our patients with RA exhibited an even higher frequency of β2-GP1 independent aCL than that reported in the letter. As expected from reported data, the presence of β2-GP1 independent aCL was not associated with signs of APS in our patients. We also found that the addition of β2-GP1 (10 μg/ml) lowered the binding of β2-GP1 independent aCL by about 50%, most probably owing to the competition between β2-GP1 independent aCL and β2-GP1 for the same binding sites on cardiolipin.

In conclusion, patients with RA may have anti-β2-GP1 and β2-GP1 dependent aCL which might be associated with the signs of APS. The importance of distinguishing β2-GP1 independent aCL has not been fully clarified. It seems that β2-GP1 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 provide some information to the data published earlier in the Annals.1

The term “anticardiolipin antibodies” (aCL) is classically used to designate antibodies directed against the cardiolipin antigen and detected in sera by the dependance of aCL on β2 glycoprotein I (β2-GP1) is assessed by an enzyme linked immunosorbent assay (ELISA) test using exogenous β2-GP1 in blocking buffer (containing fetal calf sera or bovine sera). In our previous study, this solution did not contain bovine or calf sera but only purified bovine serum albumin. So, this method was adapted to detect antibodies directed against cardiolipin antigen alone and not against the complexes of cardiolipin bound to exogenous β2-GP1. This method justified the terminology of β2-GP1 independent aCL for sera containing aCL without anti-β2-GP1 antibodies. The absence of anti-β2-GP1 antibodies was shown by another ELISA test specific for the detection of these antibodies. Both ELISAs were used to screen all sera.

The concentration of exogenous β2-GP1 contained in human serum is not significant at a 1:100 dilution (the dilution employed to screen our sera), in comparison with the 10% of calf sera added to the test as source of exogenous β2-GP1 in the assays used for the detection of β2-GP1 dependent aCL. In addition, the sera containing aCL (detected by an ELISA without addition of exogenous β2-GP1) did not react with β2-GP1 in the other ELISA test specifically designed to detect anti-β2-GP1 autoantibodies, and therefore which could detect hypothetically high titres of anti-β2-GP1 antibodies contained in these sera.

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

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

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

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

In contrast with the report of Ambrozic et al., we did not find raised levels of aCL or anti-β2-GP1 antibodies in normal sera. A percentage of positive normal serum samples was <3%. These differences between our results and those of Ambrozic et al. are probably associated with a differing sensitivity and specificity of the methods between the two laboratories.

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References


Methotrexate and postoperative complications

Grennan et al report the safety of continued methotrexate in the perioperative period.1 Previous investigators have despaired of answering this question definitively owing to the difficulty in recruiting subjects.2 It is reassuring to see that methotrexate use throughout the postoperative period does not interfere with wound healing or increase the incidence of 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.3 This, indeed, is a community based, observational study of methotrexate use in 460 patients we found the

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periorperative period to be especially hazardous for patients with renal impairment and sepsis.10 Two subjects developed pancytopenia under these conditions, one of whom died.

Although all consecutive patients were included in the study by Brennan et al., it is unclear whether Wrightington Hospital is a tertiary referral centre. Renal impairment is an important comorbidity, although no comment is made on 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.11

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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.12

A 22 year old woman presented with 18 months of a waddling gait disturbance, and difficulty standing up from a low chair and holding her arms up to allow her head 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 phosphate of 1375 U/l (normal 30–120 U/l), reduced red blood cell flocate level of 290 mmol/l (>300 mmol/l), corrected calcium of 1.75 mmol/l (2.15–2.65 mmol/l), phosphate 1.00 mmol/l (0.81–1.4 mmol/l), 25-hydroxy vitamin D <5 nmol/l (15–110 nmol/l, and raised parathormone 53.1 pmol/l (1.0–6.5 pmol/l).

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

A bone scan demonstrated increased activity throughout the skeleton, consistent with secondary hyperparathyroidism. Osteoporosis was demonstrated by dual emission x-ray absorptiometry estimation of bone mineral density, with the lumbar spine measuring 0.882 g/cm² (2.65 SD below the young adult female mean) and the neck of the femur 0.633 g/cm² (2.9 SD below the mean).

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

Within two months her bone pain and tiredness resolved and her strength had returned to normal. Calcium was within the normal range, and alkaline phosphate reduced to 374 U/l. Bone mineral density had increased markedly after 12 months of treatment, with the lumbar spine increasing by 37% to 1.204 g/cm² (mean level for young adult women), and the neck of the 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 1965,13 there have been several more case reports of coeliac disease presenting with bone pain, proximal myopathy, radiographic findings of pseudo fractures and Looser’s zones, or secondary hyperparathyroidism evident on bone scan.14 Most patients were middle aged males, 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.15 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.16

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.17 Secondary hyperparathyroidism can develop if this is not in the case, causing increased bone turnover.18 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.19

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 antientomysial antibodies. They have a high sensitivity and specificity, with a negative predictive value of around 95%.20 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/DR7.21

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.22 The change is due to improvement of calcium and vitamin D status, leading to remineralisation of the large volume of unmineralised osteoid matrix.23 An introduction of hormone replacement therapy in women approaching the menopause, and bisphosphonates in patients with osteoporotic fractures, should also be considered.24

Osteomalacia presenting with muscle weakness and aches may be the only presenting features of coeliac disease. Prompt treatment and diagnosis is important because treatment with a gluten-free diet and medication therapy including vitamin D may lead to rapid and effective recovery.25

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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 immune responses, particularly peripheral blood mononuclear cells (PBMCs) levels of Zn.

In a previous study we measured levels of Zn and Cu in PBMCs, peripheral blood mononuclear cells; there was no correlation between age, duration of disease and plasma or PBMC Cu levels. The more 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 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 back to those seen in controls. Hence, further studies need to be carried out on paired samples in a cohort of patients, once the disease is active and again when it becomes inactive. If plasma and PBMC 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


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

The relevance of monoclonal gammapathy in relation to rheumatic disorders has recently been reviewed. Monoclonal gammapathy or

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

<table>
<thead>
<tr>
<th></th>
<th>Active RA</th>
<th>Inactive RA</th>
<th>Overall RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma zinc (µg/l)</td>
<td>687 (467)</td>
<td>982 (264)</td>
<td>824 (386)</td>
<td>1024 (428)</td>
</tr>
<tr>
<td>PBMC zinc (µg/10^6 cells)</td>
<td>135.2 (28.6)</td>
<td>108.3 (38.4)</td>
<td>121.4 (34.4)</td>
<td>98.4 (16.4)</td>
</tr>
<tr>
<td>Plasma copper (µg/l)</td>
<td>1646 (357)</td>
<td>1016 (296)</td>
<td>1426 (324)</td>
<td>946 (446)</td>
</tr>
<tr>
<td>PBMC copper (µg/10^6 cells)</td>
<td>58.0 (43.2)</td>
<td>86.4 (33.2)</td>
<td>74.3 (38.2)</td>
<td>104.2 (8.5)</td>
</tr>
</tbody>
</table>

PBMCs, peripheral blood mononuclear cells; there was no correlation among age, duration of disease, rheumatoid factor positivity, or any other single drug or plasma or PBMC levels of Zn and Cu.

*Overall levels were significantly lower among patients than controls (p<0.05) and patients with active RA had lower levels than those with inactive RA (p<0.05). Toverall levels were significantly higher in patients than controls (p<0.05) and patients with active RA as compared with those with inactive RA (p<0.05). There was overall a negative correlation between plasma and PBMC zinc levels (p<0.05); toverall, patients with RA had higher levels than controls (p<0.01) and those with active RA had higher levels than those with inactive disease (p<0.01). toverall, patients with RA had lower levels than controls (p<0.01) and those with active RA as compared with those with inactive disease (p<0.01). There was a negative correlation between plasma and PBMC copper levels (p<0.05).
paraproteins can be detected in healthy adults and in different disease entities like amyloido-
sis, malignant proliferative disorders, 7 associa-
ted with hepatitis C infections, 8 and rheu-
matic diseases. 9 The overall incidence of para-
proteins in adults is about 1%. 10 This inci-
dence is higher in people over 70 and increases with age. 11 When a paraprotein is de-
ected and no underlying disease is present, the
condition is referred to as a monoclonal gam-
mopathy of undetermined significance.
Owing to their immunological proper-
ties, 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 coexist-
ence of paraproteins. Recently, three patients
with a clinical picture of a necrotising vasculi-
tis associated with an essential cryoglobuli-
naemia (type 1) were admitted to our depart-
ment. The causative relationship between the
cryoglobulinaemia and the clinical symptoms
was restricted 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
foot became necrotic. Angiography of his
hand. In the following days the upper part of
her foot the necrosis began to demarcate to the
necrotising vasculitis was seen. He was
treated with chlorambucil 8 mg daily, which
after two weeks was switched to melphalan (6
mg/m²) and prednisone (60 mg/m²) every four
weeks for six months. The M component fell
to 2 g/l and the severe Raynaud's phenom-
ena disappeared.
Patient C was a 78 year old woman who was
admitted to our hospital in May 2000 with
cyanosis in both feet, indicating possible arte-
rnal occlusion. Depending on the cold feet were
cold and very painful. Angiography showed nor-
mal vessels, which strongly suggested vasculi-
tis of the end arterial vessels of her feet.
Laboratory examination showed a parapro-
tein (8 g/l) combined with a cryoglobulinae-
ia consisting of the monoclonal protein (IgGA). Other laboratory examinations
showed no abnormalities. Virus serology
showed only a positive cytomegalovirus titre.
She was treated with chlorambucil (8 mg/
day) and prednisone (60 mg/day), which
improved the necrosis of her legs. The necrosis
of her right leg disappeared and on the left
foot the necrosis began to demarcate to the
upper part of her foot. While waiting for the
complete demarcation so that an amputation
could be planned, she developed a sepsis and
died.
Few patients with essential cryoglobulinae-
ia type 1 have been reported. Until now a
defined clinical syndrome could never be
associated with classification of the cryo-
globulins. 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 angio-
graphic examination, which may indicate that
only the small vessels are affected in the
disease process.
In our patients we were able to show that
the cryoglobulins were formed by the mono-
clonal immunoglobulin. When the serum
concentration of the cryoglobulins was re-
duced, the disease symptoms in our patients
improved. These cases suggest that a parapro-
tein found in patients with a rheumatic
syndrome is not only indicative of a develop-
ing malignancy but other disease may also
be interpreted as a causative agent. We
conclude that paraproteins seen in rheumatic
syndromes have a role in the pathogenesis and
should be treated when serious symp-
toms are present.

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Cryoglobulinemia vasculitis as
presenting manifestation of
infective endocarditis
Serum immunological alterations, including
antibodies and/or cryoglobulins, are common
in infective endocarditis (IE). However, spe-
cific autoimmune diseases, such as cryoglobu-
ilnaemia vasculitis (CV) associated with IE
have seldom been described. 12 CV is related
to the vascular deposition of circulating immune
complexes, mainly cryoglobulins, and comple-
ment 5; in 70–90% of patients with CV a trigg-
ering role of hepatitis C virus (HCV) has
been suggested. 13 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
admitted with fever, purpura, paraesthesiae,
and pseudoaxial gait. Her past clinical his-
tory was unremarkable except for a pros-
thetic implant of the left hip four years previ-
ously. Table 1 shows the main clinico-accordion-
ial features. Repeated blood cultures were
negative. Neurological examination showed
abnormal tactile sensation in arms and legs;
mild ideomotor slowing down; shaky
movements; and unsteady gait. An electro-
physiological study recorded a moderate sen-
sorimotor peripheral neuropathy, while chest x
ray examination, abdominocgraphy, and
echocardiography were normal. Cutaneous
purpura biopsy disclosed a leuco-
cytoclastic vasculitis. Truncocerephalic mag-
etic resonance imaging showed a focal
weighted high signal intensity, punchiform
lesions at the white matter consistent with
brain vasculitis. Thus a central and peripheral
neuropathy complicating CV was established,
and prednisone (50 mg) combined with
cyclophosphamide (100 mg) was given daily.
However, the patient's clinical status progres-
sively worsened and, finally, she died owing
to cardiorespiratory failure during the first
month of treatment. Necropsy disclosed
 coarse endocardial vegetations on the left
sided valves infected by 

Case 2
In January 1999 a 75 year old woman with no
risk factors for infections presented with fever,
purpura, and acaraparaphyptes. 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, arthritis, acaropal-
aesthesia, and impairment of distal muscle
strength. An electrophysiological study con-
ﬁrmed a sensorimotor peripheral neuropathy.
Thus a higher steroid dose (50 mg/day) was
given. A week later fever persisted and the
patient complained of precordial pain and
cardiac murmurs were found. A chest x
ray examination, and transoesophageal echocar-
diography detected cardiomegaly and en-
doconal 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 sepsis and
 refractory heart 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 chiefly prevalent CV symptoms appear 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 “asymmetric” cryoglobulinaemia is not uncommon, but only a few studies report IE clinically presenting as CV. This latter presentation can mean a differential diagnosis more often, 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 linked immune system involvement, 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, but the aetiopathogenesis of which is still unclear. In a considerable number of patients with IE negative blood cultures have also been recorded, often when Gram negative bacteria are involved.

In patient 1, the lack of timely recognition of Kingella by repeated blood cultures was probably due to different reasons, including slow growing of the agent, low microbial load, probably due to different reasons, including slow growing of the agent, low microbial load, probably due to different reasons, and/or inappropriate use of growth media. However, the negative cultures together with clinical symptoms suggestive for CV, in the absence of relevant features at transcranial 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 clinicomicrobiological evaluation, including transoesophageal echocardiography.

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

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>Disease duration (weeks)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>Severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Recurrent</td>
<td>Constant</td>
</tr>
<tr>
<td>Hepatopathy</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>Peripheral</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Cardiac symptoms</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>CRP (normal &lt;5 mg/l)</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>WBC (normal 5–10 ×10^9/l)</td>
<td>89 000</td>
<td>83 600</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>γ Globulinemia (g/l)</td>
<td>19.5</td>
<td>21.3</td>
</tr>
<tr>
<td>RF (normal &lt;20 IU/ml)</td>
<td>575</td>
<td>137</td>
</tr>
<tr>
<td>C3 (normal 500–1200 mg/l)</td>
<td>930</td>
<td>790</td>
</tr>
<tr>
<td>C4 (normal 200–550 mg/l)</td>
<td>&lt;60</td>
<td>100</td>
</tr>
<tr>
<td>Cryocrit, % (cryo-type)</td>
<td>0.5 (IgG-IgM)</td>
<td>2 (IgG-IgM)</td>
</tr>
<tr>
<td>Hepatitis virus markers</td>
<td>Negative</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.

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. 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.

We retrospectively examined 35 serum samples from patients with Graves’ disease. ANCA, a diffuse granular cytoplasmic staining with central accentuation, was seen, as pANCA, when a perinuclear pattern was observed, and as nANCA when a cytoplasmic staining pattern was seen. Autoantibodies against proteinase 3 and myeloperoxidase (MPO) were detected by enzyme linked immunosorbent assay (ELISA; Organetic) as described elsewhere. Hospital Universitari Germans Trias I Pujol is a 553 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%) nANCA, 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 Afetra 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 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.
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.13

There is a need to determine the autoantigenic 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 antinuclear drugs (thiazomazole or propylthiouracil) or to the disease itself.

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 emphasize the role of prostaglandins in the cytokine induction and modulation of the humoral immune response.15 We present a patient with systemic lupus erythematosus (SLE) who had a relapse after prostaglandin E (PGE), administration, which to our knowledge has not been previously reported.

A 25-year-old woman was admitted to hospital to receive treatment with IV PGE, owing to severe Raynaud’s phenomenon. Fifteen years previously SLE had been diagnosed according to American Rheumatism Association (ARA) criteria, with renal biopsy showing diffuse proliferative lupus glomerulonephritis (WHO class IV). A physical examination showed only painful, violaceous, and atrophic changes in the rest of the biochemical serum parameters. Echocardiography and 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 films showed moderate pericardial and bilateral pleural effusions. PGE, was withdrawn and prednisone, 60 mg/day, was started with prompt improvement in the symptoms.

We investigated the possibility that PGE, mediated cytokine production might be the cause of the relapse of SLE in this patient. Intracellular expression of cytokines in the patient’s T lymphocytes after specific PGE, stimuli (10 ng/ml) was determined by flow cytometry using anticytokine conjugates in combination with surface anti-CD3 (Pharmingen, San Diego, CA), as previously described.16 The test performed eight months after the PGE, treatment showed a dramatic rise in interleukin-4 (IL4) production (table 1). It has been suggested that cytokines have an important role in the immune dysregulation seen in lupus prone mice and in patients with SLE. Increasing evidence supports a role in vivo in this patient, may be a marker of dysregulation of the Th1/Th2 profile and might have been the cause of her lupus relapse.

REFERENCES


Table 1 Intracellular cytokine production after 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>INFγ</th>
<th>IL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>Basal</td>
<td>PGE</td>
</tr>
<tr>
<td>Patient</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Control</td>
<td>0.8</td>
<td>0.6</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.

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Acknowledgment

This study was sponsored by a grant from the Catalan Society for Rheumatology.
Osteocalcin: a marker of disease activity in ankylosing spondylitis?

In rheumatic diseases the synovial concentration of osteocalcin, which represents osteoblastic 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 11 years; disease duration 19 years) venous blood was taken at the start and the end of a three week rehabilitation course consisting of physical exercise, physiotherapy, electrotherapy, underwater exercises, and raton treatment as prescribed by the patient's doctor. Patients were advised not to change their drug treatment. The ESR was determined according to a standard procedure, the result at one being used for calculation. Serum was frozen at −18°C until further analysis. Osteocalcin was measured in one batch with a commercially available test kit (IRMA, Biocis, Vienna; normal range according to the manufacturer 7.5–31.5 ng/ml in men, 3.7–31.7 ng/ml in women). Results are given as median (25th, 75th centile). The Mann-Whitney rank sum test and Spearman rank order correlation test were used to test significance.

Values at the first measurement were ESR 18 (8, 28) mm/1st h, serum osteocalcin 25 (20.5, 32.8) ng/ml. The osteocalcin serum concentration was within the normal range in 66 of the 89 patients, and 23 patients had increased serum concentrations. Values at the end of treatment were ESR 16 (8, 26.5) mm/1st h, osteocalcin 26.1 (18.9, 32.7) ng/ml (no significant changes). The ESR and osteocalcin at the first examination did not correlate significantly (r=0.07; p=0.5). The changes in ESR (1 to 4, 6 mm/1st h) and changes in osteocalcin (−0.5 to 2.6, 5.7) ng/ml showed a significant correlation (r=−0.28; p<0.01).

The results confirm previous findings showing no significant correlation between serum osteocalcin and ESR in cross sectional studies. Changes in osteocalcin after three weeks, however, correlated significantly with changes in ESR, but in view of the weak correlation (r=0.28) the clinical relevance of serum osteocalcin determination for assessment of disease activity seems limited.
CD4+ lymphopenia may cause dysgammaglobulinemia and autoimmune syndromes such as Takayasu arteritis.

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References

CD4+ lymphopenia is rare in adults and even rarer in children. It is rare for patients to have both disorders and with this case report, we draw attention to this association. This case report suggests that low

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

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. Among the patients with 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 has been less than 0.4 × 10^9/l to determine the natural history of their infections and lymphocyteopenia. Two recent preliminary reports suggest the presence of a retrovirus in affected patients, but conclusive evidence is lacking. The investigations of cases of idiopathic depletion of CD4+ T lymphocytes indicate that they probably represent various disorders, and that in some cases, low CD4+ T lymphocyte counts may reflect transient responses to infections or other conditions such as autoimmune disorders. In patients with aortitis arteritis, immunological investigations have shown a decrease in the titre of complement and phagocytic activity of neutrophil granulocytes, deep depression of T cell immunity, and hypogammaglobulinemia. Wiskott-Aldrich and Takayasu arteritis have been reported previously. It is rare for patients to have both disorders and with this case report, we draw attention to this association. This case report suggests that low

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 clinical 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 (20 mg/kg/day) and systemic corticosteroid treatment (prednisone 1 mg/kg/day, tapered and withdrawn after 15 days); symptoms recovered completely in two weeks. A first magnetic resonance imaging (MRI) scan of the orbit had shown severe ocular pain and diplopia, lasting from two to four weeks, affecting both eyes or alternatively the right and the left, at intervals of three months. No sequelae were detected after each relapse.

During the last relapse in October 1999, naproxen and high dose oral corticosteroid treatment (prednisone 2 mg/kg/day) were required to control the disease activity, which subsided over a period of two months. After a short period of wellbeing, the disease flared up again, and recurrence of orbital pain and diplopia was observed when steroids were reduced to 0.5 mg/kg/day. The boy was then admitted to our unit. He appeared well, with no constitutional symptoms. Ocular examination showed mild right exophthalmos and limited motion of both eyes.

Laboratory tests including muscle enzymes (alanine aminotransferase), aspartate aminotransferase, creatine kinase, lactate dehydrogenase, aldolase) values, complement levels, and thyroid function were all within the normal range. Serological tests were negative for viral and bacterial infections, and antibodies against Borrelia burgdorferi were absent. Autoantibodies (antinuclear antibodies, anti-dsDNA, anticardiolipin, antinuclear nucleic antigens, peri-nuclear antineutrophil cytoplasmic antibodies) were undetectable. Other markers that are considered measures of disease activity in juvenile inflammatory myopathies were evaluated: factor VIII related antigen levels were raised, while neopterin levels and the number of circulating B lymphocytes (CD19 positive cells) were normal. Electrocardiography and two dimensional echocardiography excluded a concurrent myocarditis. On the basis of clinical manifestations and immunological parameters systemic lupus erythematosus (SLE), scleroderma (Scl), Crohn’s disease, and thyroiditis were excluded. Orbital MRI showed significant oedema and thickening of the left extrinsic and of the right medial rectus muscles. Electromyography showed increased insertional activity, fibrillations, and positive sharp waves. Ocular myositis was diagnosed. The oral prednisone dose was raised to 30 mg/day, and rapidly tapered after improvement of signs and symptoms. In November 2000, cyclosporin (3 mg/kg/day) was introduced; no relapse of the ocular findings has been seen so far, and prednisone has been progressively reduced to the current dose of 5 mg/day.

The group of idiopathic inflammatory myopathies encompasses a variety of common and uncommon syndromes. The uncommon variants of myositis include orbital myositis, a condition that is rare in adults and even rarer in children. Orbital muscle inflammation may be seen in association with other autoimmune diseases, such as SLE, Scl. giant cell myocardiitis, and Crohn’s disease. Primary conditions that it is important to distinguish from orbital myositis include thyroid eye disease; ocular myopathies, such as mitochondrial disorders and 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

Figure 1 Orbital MRI (T1, weighted image with contrast) that shows increased signal and size of the right rectus lateralis muscle.

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Hodgkin's lymphoma is rare. The involvement of the central nervous system is unusual and extensive investigation that must include isolated ocular myositis in the differential diagnosis.

**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 the left lumbosacral spinous processes. Straight leg raising test was restricted to 45° bilaterally, and produced lumbar pain. Neurological examination of the legs showed normal tone, power, and coordination. Knee jerks were reduced, ankle jerks were absent, both plantars were down going, and there was no sensory deficit.

He had a past history of epilepsy, which was controlled by phenytoin and phenobarbitone. In 1993 he was admitted with abdominal pain, splenomegaly, and pancytopenia; this was diagnosed as low grade B cell lymphoma and hyperplenism. Splenectomy was performed in 1994; his blood count returned to normal, and repeated full blood counts were stable. In 1995 he 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 and degenerative changes.

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 24.7×10⁹/l, differential count showed neutrophils 3.5×10⁹/l (14%), lymphocytes 17×10⁹/l (69%), monocytes 4.0×10⁹/l (16.0%), eosinophils 0.2×10⁹/l (1.0%), basophils 0.0×10⁹/l (0.0%), and occasional atypical lymphocytes were seen in blood film. The erythrocyte sedimentation rate was 4 mm/1st h, a myeloma screen was negative, and prostate specific antigen was normal.

A lumbosacral spine x-ray examination showed biconcave L5 with diffuse osteopenia. Abdominal ultrasound confirmed splenectomy, but no enlarged lymph nodes were detected. A bone isotopic scan showed increased focal activity in the upper lumbar spine and lumbosacral junction, which was compatible with osteoporosis and degenerative changes.

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

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

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

In rheumatology, it is essential to differentiate between non-Hodgkin’s lymphoma 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 of rheumatologic disorders, our patient was considered to be a candidate for further investigation.

**Scanning of the spine**

A sagittal MR scan of the spine showing vertebral infiltration, being most intense in L2 and L5, which is biconcave (arrows).

**Unusual complications in the Churg-Strauss syndrome**

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

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

**Figure 1**

Sagittal MR scan of the spine showing vertebral infiltration, being most intense in L2 and L5, which is biconcave (arrows).
Two and six weeks later she was readmitted owing to right upper quadrant pain. The leucocyte count was $1 \times 10^9$/l with 34% eosinophils. Abdominal ultrasonography and computed tomography (CT) scan showed acalculous cholecystitis. A laparotomy disclosed a purulent peritoneal collection and enlarged inflamed gall bladder and right ovary. A cholecystectomy and right anexectomy were performed.

One month after surgery she was readmitted with severe abdominal pain, diarrhoea, and fever. The leucocyte count was $4.89 \times 10^9$/l with 22% eosinophils, erythrocyte sedimentation rate (ESR, Westergren) 39 mm/1st h, rheumatoid factor (RF) 765 IU/ml (normal <80), and total IgE 769 IU/ml (normal <100), and serum urea and creatinine, complement C3 and C4, antinuclear antibody and antineutrophil cytoplasmic antibody values were normal or negative. The urine contained 300 mg/l proteins and the sediment 6–8 red cells, hyalinogranular casts. An abdomen CT scan showed moderate ascites. The ascitic fluid, rich in eosinophils, showed moderate ascites. The ascitic fluid was serofibrinous with a protein concentration of 55 g/l, a leucocyte count of $1.05 \times 10^9$/l with 44% eosinophils, and negative standard and Lowenstein cultures. A diagnosis of CSS was made after reviewing the previous gallbladder and ovarium histopathological specimens (fig 1) and considering the history of asthma, eosinophilia, and nasal polyposis.

Oral methylprednisolone 60 mg/day and cyclophosphamide 100 mg/day were started, with initial clinical improvement. However, the abdominal pain recurred and the patient underwent a second laparotomy after three weeks of treatment. Peripheral blood leucocytes were $18.1 \times 10^9$/l with 1% eosinophils. Blood urea, creatinine, and urinary sediment were normal, the ESR fell to 15 mm/1st h and the RF to $435 \mu$g/l. Purulent fluid in the peritoneal cavity and two perforations in the ileal wall were found. Bowel histology showed wall ulcerations, vascular thrombosis with fibrinoid necrosis, and eosinophil infiltrates. Granulomas were not found. E coli grew from the peritoneal fluid. Intravenous metronidazole and gentamicin were started. Four days later a new perforation was suspected and a third laparotomy was done, showing a perforated necrotic small bowel plaque. A broad bowel resection was performed but the patient’s evolution was complicated with high fever, ileus, and vomiting, and she died 48 hours later. A necropsy was not allowed.

Abdominal pain is reported in up to 25–59% of cases of CSS, although many times the cause is unknown. Gastric and colonic ulcers, intestinal fistulas, and small bowel perforations have been described, the last of these being responsible for up to 10% of the CSS deaths. 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 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. Eosinophil 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.
20nd European Workshop for Rheumatology Research
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International Congress: New Trends in Osteoarthritis
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10–14 May 2002; Lisbon, Portugal
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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
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