Joint restriction in an unhappy teenager

P J C Davis, J Hackett, K Johnson, J E McDonagh


A 14 year old girl presented with a year’s history of joint pain, restriction, and swelling, initially diagnosed as juvenile idiopathic arthritis. She had no past medical problems but had given up her leisure pursuits owing to disability. Examination disclosed non-pitting oedema to mid-calf; a woody texture of the soft tissues of the forearms and calves with fixed flexion deformities of her fingers, wrists, knees, and ankles due to the soft tissue changes, and normal overlying skin. Investigations showed the following results: normal muscle enzymes, eosinophilia of 1.7×10^6/L, erythrocyte sedimentation rate 41 mm/1st h, haemoglobin 112 g/L, negative autoantibodies, and normal complement levels. The differential diagnosis included eosinophilic fasciitis (EF) and scleroderma. At this time, the patient requested counselling as she had difficulty accepting an initial misdiagnosis, delayed correct diagnosis, and the uncertainty of the prognosis.

Magnetic resonance imaging (MRI) of the forearm was performed (fig 1). A biopsy showed chronic inflammatory changes in the deep subcutaneous fat and fascia with infiltration by lymphocytes, plasma cells, histiocytes, and eosinophils. The fascia was markedly thickened and fibrosed with focal fibrinoid necrosis, consistent with EF.

In view of her disability, she was treated with intravenous methylprednisolone (1 g/day for 3 days), then oral prednisolone 20 mg daily (0.3 mg/kg/day) with normalisation of her erythrocyte sedimentation rate and eosinophilia. Methotrexate 15 mg orally weekly was added 2 months later as there had been no further significant clinical response to steroids.

Five months later she improved functionally with reduced contractions despite prednisolone reduction to 12.5 mg daily. A repeat MRI scan showed a reduction in the subcutaneous and fascial oedema, prompting a further reduction in steroids. At this time, she self harmed by cutting the skin of her forearms because of low mood, difficulties adjusting to her diagnosis, and the cosmetic side effects of steroids. She required treatment with antidepressants and counselling.

One year after diagnosis, an MRI scan showed persistent fascial oedema, leading to an increase in methotrexate (17.5 mg orally weekly) while maintaining her prednisolone at 3 mg daily. Over the following 6 months finger movement improved despite stopping prednisolone in the interim. However, she attempted suicide by taking an overdose of methotrexate as she felt a burden to others, and required further psychological treatment.

Three years after diagnosis, she remains well and continues to receive methotrexate, with minimal inflammation on MRI, mild finger and wrist contractures, and return of full function. At no time has there been evidence of internal organ involvement.

EF is characterised by painful swelling and stiffness of the extremities, typically with thickened skin (peau d’orange), a peripheral eosinophilia, and characteristic histology.1 2 3 4 In contrast with adult EF, paediatric EF predominately affects girls and has not been reported to cause haematological complications. In contrast with scleroderma, the epidermis and dermis are spared, whereas in comparison with polymyositis there is minimal muscle inflammation, distinctions illustrated by MRI.1 2 3 5

Teenage self harm is well recognised, particularly in girls, although may be underdiagnosed in those with a chronic illness.6 The impact of the disease itself, its impact upon body image and lifestyle, and the side effects of treatment, lack of predictability, and uncertainty of prognosis are all likely to contribute to mental health status during adolescence.5

Prognosis in paediatric EF remains uncertain, although a previous study has reported more favourable outcomes in older children.7 We expect to withdraw methotrexate from this girl within the next 12–18 months if her signs and MRI appearance remains stable. This case highlights the use of MRI in assessment of soft tissue disease and in guiding drug management. Furthermore, the psychological impact during adolescence of a chronic disease, its management, and correct diagnosis should not be underestimated.

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Figure 1 Coronar short t inversion recovery (STIR) image of arm. The white arrows indicate areas of high signal oedema within the fascia.
Relapse of autoimmune diseases after autologous T cell depleted stem cell transplantation may be triggered by T cells recently emigrated from the thymus

I Köttner*, T Daikeler*, H Einsele, S Koch, L Lochmann, L Kanz, J Löffler


High dose immunosuppressive therapy with subsequent autologous stem cell transplantation (ASCT) has proved effective for treatment resistant autoimmune diseases. However, in a number of patients, relapses of autoimmune disease after initial improvement or even remission occur. Until recently, it was impossible to differentiate recent thymic emigrants from residual or peripherally expanded T cells. Douek and coworkers and later our group described a method for detection of T cell receptor excision circles, stable DNA episomes which are formed during T cell receptor rearrangement in the thymus which are not replicated during mitosis, but are diluted during cell divisions. This study aimed at investigating whether these flares are associated with de novo T cell development.

Peripheral blood mononuclear cells were collected from six patients, mean age 32.5 years, range 24–42 (four with systemic sclerosis (SSc), one with Wegener’s granulomatosis (WG), one with mutilating psoriatic arthritis (PsA)), after high dose immunosuppression with cyclophosphamide 50 mg/kg body weight plus anti-thymocyte globulin 20 mg/kg on days 1–4, with subsequent retransfusion of 4.2 × 10^6 (median) CD34+ selected (by CliniMacs device) cells/kg body weight. Blood collection was performed at week 2 and then, at bimonthly intervals, genomic DNA was extracted using the QIAmp DNA Blood Mini Kit. DNA was stored at −80°C until analysis. T cell receptor rearrangement excision circles (TRECs) were measured by real time polymerase chain reaction using the light cycler (Roche Diagnostics Corporation, Idaho, USA). The study was approved by the local ethics committee and patients’ informed consent obtained.

All patients improved considerably (all patients with SSc) or went into remission (PsA, WG) after ASCT. In all patients, previous immunosuppressive therapy was discontinued, except in the patient with WG, who still received ciclosporin A for her kidney transplant. Two patients relapsed after 7, and 19 months, respectively (one SSc, one PsA). CD3+CD4+ T cells were recovered after 6–14 months (median 12), and CD3+/CD8+ T cells a maximum of 3 months after ASCT in all patients. Autoantibodies disappeared in four of five patients after a median of 6 months and their recurrence or disappearance later did not correlate with relapse or remission. TRECs could not be detected in the patients shortly after ASCT (week 2), but recurred 9–26 months (median 16 months) after ASCT. In the two patients who experienced relapses, TRECs became detectable at the time when the first symptoms of relapse were noticed (SSc, patient No 3: relapse after 7 months, TRECs after 9 months; PsA, patient no 4: relapse after 19, TRECs after 21 months—the blood collection did not always coincide exactly with the diagnosis of relapse, which explains the 2 months’ difference between diagnosis and first detection of TRECs) (fig 1, table 1).
<table>
<thead>
<tr>
<th>Patient No</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
<th>Week 60</th>
<th>Week 72</th>
<th>Week 90</th>
<th>Week 106</th>
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<th>Week 172</th>
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<td>7850</td>
<td>6740</td>
<td>8880</td>
<td>6880</td>
<td>11540</td>
<td>ND</td>
<td>8860</td>
<td>11470</td>
<td>7030</td>
<td>5430</td>
<td>7290</td>
<td>10210</td>
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<td>Lymphocytes (%)</td>
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<td>3</td>
<td>29.6</td>
<td>18.8</td>
<td>20.8</td>
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<td>9.9</td>
<td>14.5</td>
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<td>17</td>
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<td>28</td>
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<td>CD8 (%)</td>
<td>1</td>
<td>27</td>
<td>4</td>
<td>44</td>
<td>45</td>
<td>42</td>
<td>ND</td>
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<td>30</td>
<td>31</td>
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<td>ND</td>
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<td>CD20 (%)</td>
<td>1</td>
<td>0.3</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>ND</td>
<td>10</td>
<td>ND</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td>15</td>
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<tr>
<td>CD56 (%)</td>
<td>1</td>
<td>6</td>
<td>21</td>
<td>4</td>
<td>4</td>
<td>5</td>
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<td>cANCA</td>
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<td>ND</td>
<td>cANCA</td>
<td>cANCA</td>
<td>Neg</td>
<td>ND</td>
<td>cANCA</td>
<td>cANCA</td>
<td>cANCA</td>
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<tr>
<td></td>
<td>2</td>
<td>ANA</td>
<td>ANA</td>
<td>Nucleoli</td>
<td>ANA</td>
<td>Nucleoli</td>
<td>SC-70+</td>
<td>ND</td>
<td>ND</td>
<td>cANCA</td>
<td>ANA</td>
<td>Neg</td>
<td>ND</td>
<td>cANCA</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Nucleoli</td>
<td>Nucleoli</td>
<td>Nucleoli</td>
<td>Nucleoli</td>
<td>Nucleoli</td>
<td>Nucleoli</td>
<td>ND</td>
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<tr>
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<td>4</td>
<td>None</td>
<td>ND</td>
<td>ND</td>
<td>Unspecific</td>
<td>ND</td>
<td>Unspecific</td>
<td>Neg</td>
<td>Unspecific</td>
<td>Neg</td>
<td>ND</td>
<td>ND</td>
<td>Neg</td>
<td>Unspecific</td>
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</table>
Normally, immune reconstitution and TREC recurrence is considerably quicker in ASCT than in allogeneic SCT. TREC recurrence in the allogeneic setting is known to be delayed by clinical events such as graft versus host disease, whereas in ASCT CD34+ selection of the graft was associated with increased thymic output ("rebound phenomenon"). In the present study, T cell ontogenesis was delayed even in comparison with allogeneic SCT for haematological diseases (TREC recurrence: 6 months). Premature immunosenescence may be one of the reasons for this delay in T cell ontogenesis after ASCT in autoimmune diseases.

De novo T cell ontogenesis in the thymus may be a critical event inducing relapses of the autoimmune disease, which may not be caused by peripheral expansion of memory T cells which survived the conditioning treatment, but by newly developed T cells of thymic origin. Vice versa, as in four patients TRECs recurred without relapse of the autoimmune disease, one might also argue that the occurrence of TRECs is not causally associated with relapse. Further studies of the immune reconstitution, correlating the recurrence of TRECs with T cell subsets, T cell receptor diversity, and autoantibody production in patients with autoimmune diseases after ASCT will improve our understanding of the pathogenesis of these diseases and help in the development of new therapeutic concepts.

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Rheumatoid arthritis (RA) is a T cell mediated autoimmune disease and associated with HLA-DR4 or HLA-DR1 subtypes. Type II collagen (CII) has been implicated as an autoantigen of RA, and CD4+ T cell responses to CII or CII derived peptides are mainly presented by HLA-DR4/1 molecules. Inhibition of antigen presentation by HLA-DR4/1 molecules can interfere with T cell mediated autoimmune responses in RA.

Our previous studies have suggested that altered CII263–272 peptides inhibited CII263–272-induced T cell activation by blocking antigen presentation. In this study we examine the role of the altered influenza virus haemagglutinin (HA) 308–317 peptides (altered peptide ligands (APLs)) with single or multiple substitutions of T cell receptor (TCR) contact residues in T cell responses of peripheral blood mononuclear cells (PBMC) and inhibitory effects of APLs on CII263–272-induced T cell activation in RA.

Twenty seven HLA-DR4/1 positive patients with RA (21 female, 6 male; mean (SD) age 53.6 (13.3) years; mean (SD) disease duration 10.4 (8.4) years) were included in the study. All patients fulfilled the American College of Rheumatology revised criteria for the classification of RA. Of 27 patients with RA, 24 (89%) were positive for DR4 and 3 (11%) for DR1.

Sequences of three APLs and CII263–272 were YVAQONTLKA (APL1), YAKQITLTLA (APL2), YAKQITLTLA (APL3), and FKGEQGPKGE, respectively. T cell proliferation experiments were performed by [3H]thymidine incorporation assay. PBMC (2.0×10^5/well) were incubated with CII263–272 or APLs at 10 µg/ml for 5 days. In competitive studies, PBMC were preincubated with various concentrations of APLs as indicated for 2 hours before addition of CII263–272. Cultures were pulsed with [3H]thymidine (0.25 µCi/well) before the last 12 hours. The data are presented as the stimulation index (SI).

Enzyme linked immunosorbent assay (ELISA) kits were used to detect the levels of interferon γ (IFNγ) or interleukin (IL) 4 in the supernatants (table 1). To find whether the altered HA308–317 peptides affected cytokine profile, supernatants of PBMC were evaluated for IFNγ or IL4 production from 10 patients with RA with the altered HA308–317 peptides or CII263–272 stimulation. The levels of IFNγ in the supernatants from PBMC stimulated with CII263–272 were significantly higher than those incubated with medium alone (p<0.05). In contrast, APLs down regulated IFNγ production in the supernatants from PBMC, compared with CII263–272 (*p<0.05). No differences of IL4 productions in the supernatants were found when T cells in PBMC from patients with RA were stimulated with CII263–272 or APLs.

### Table 1 IFNγ and IL4 production by PBMC of RA stimulated by altered HA308–317 peptides

<table>
<thead>
<tr>
<th>Stimulators (10 µg/ml)</th>
<th>IFNγ (pg/ml)</th>
<th>IL4 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td>n = 10</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CII263–272</td>
<td>32.1 (5.8)*</td>
<td>25.9 (3.5)</td>
</tr>
<tr>
<td>APL1</td>
<td>37.8 (14.1)</td>
<td>26.5 (5.1)</td>
</tr>
<tr>
<td>APL2</td>
<td>37.2 (23.9)</td>
<td>29.6 (4.0)</td>
</tr>
<tr>
<td>APL3</td>
<td>34.8 (19.0)*</td>
<td>28.9 (6.9)</td>
</tr>
</tbody>
</table>

Results are shown as mean (SD).

To find whether the altered HA308–317 peptides affected cytokine profile, supernatants of PBMC were evaluated for IFNγ or IL4 production from 10 patients with RA with the altered HA308–317 peptides or CII263–272 stimulation. The levels of IFNγ in the supernatants from PBMC stimulated with CII263–272 were significantly higher than those incubated with medium alone (p<0.05). In contrast, APLs down regulated IFNγ production in the supernatants from PBMC, compared with CII263–272 (*p<0.05). No differences of IL4 productions in the supernatants were found when T cells in PBMC from patients with RA were stimulated with CII263–272 or APLs.

The mechanism by which APLs antagonise T cell responses cannot be based on HLA-DR blockade only. Alternatively, APLs may alter the cytokine production profile of T cells.

In this study we showed that APLs down regulated the production of IFNγ compared with CII263–272, which
promoted IFNγ secretion. These results suggest that APLs are not Th1 stimulators. It is not clear whether they regulate Th2 cells because no effects on IL4 production were found in the present study. Further studies are necessary to investigate whether APLs effectively inhibit T cell activation in vivo, such as in the HLA-DR4 transgenic animal model.

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Relationship between 5,10-methylenetetrahydrofolate reductase C677T gene polymorphism and methotrexate related toxicity in patients with autoimmune diseases receiving folic acid supplementation

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The common polymorphism C677T of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene reduces enzyme activity and it has recently been associated with increased incidence of methotrexate (MTX) related toxicity in patients with cancer and rheumatoid arthritis. Considering that folate supplementation may reduce toxicity without affecting MTX efficiency, we conducted a retrospective study to analyse the effect of this polymorphism in patients with autoimmune diseases receiving folate acid supplementation.

Sixty three patients (F/M: 44/19, mean age 53.6 years, range 20–81) with autoimmune diseases who had been treated with MTX (7.5–15 mg/week, mean duration 35.8 months, range 2–121), were selected from the outpatient clinic between January and June 2004. Five of them had discontinued MTX treatment at the time of selection, because of adverse events or inefficiency. Thirty nine of the patients were receiving a combination of MTX with corticosteroids and/or other disease modifying antirheumatic drugs. All the patients were prescribed supplementary 2.5 mg folic acid the day before and the day after MTX treatment. All participants were informed and consented to take part in the study. Table 1 shows the characteristics of the patients.

Genomic DNA was extracted from peripheral blood, and analysis of the MTHFR C677T polymorphism was performed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MTHFR genotype, %</th>
<th>Present (n = 15)</th>
<th>Absent (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>56.8 (10.8)</td>
<td>52.6 (16.6)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>33–72</td>
<td>20–81</td>
<td></td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>11/4 (2.75)</td>
<td>33/45 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>13 (88)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2 (10)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>–</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Polymyositis</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.6 (30.1)</td>
<td>35.6 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2–121</td>
<td>5–120</td>
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</tr>
<tr>
<td>Additional drugs (No (%) of patients)</td>
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<td></td>
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<tr>
<td>Corticosteroids (only)</td>
<td>2 (13)</td>
<td>7 (15)</td>
<td></td>
</tr>
<tr>
<td>Other DMARDS (≥ corticosteroids)</td>
<td>8 (53)</td>
<td>22 (46)</td>
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<tr>
<td>MTHFR genotype, %</td>
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</tr>
<tr>
<td>CC (wild type)</td>
<td>10 (67)</td>
<td>13 (27)</td>
<td></td>
</tr>
<tr>
<td>CT (heterozygous)</td>
<td>3 (20)</td>
<td>28 (58)</td>
<td></td>
</tr>
<tr>
<td>TT (homozygous)</td>
<td>2 (13)</td>
<td>7 (15)</td>
<td></td>
</tr>
</tbody>
</table>

DMARDS, disease modifying antirheumatic drugs (includes ciclosporin: 9 patients, hydroxychloroquine: 7 patients, and infliximab: 14 patients).
by polymerase chain reaction (PCR) amplification followed by restriction digestion analysis (fig 1). The statistical analysis was performed with SPSS statistical software.

The prevalence of the MTHFR C677T genotype in our cohort of patients was 37% for 677CC (23/63 patients), 49% for 677TT (31/63 patients), and 14% for 677TT (9/63 patients). Fifteen (24%) patients displayed one or more adverse effects (three nausea, eight neutropenia/pancytopenia, two a rise in transaminases, and three oral mucositis) and six of them discontinued MTX because of toxicity. Moreover, a further four patients discontinued MTX, one because of inefficiency, one because of emergence of secondary myeloidosis, and two because of emergence of neoplasia (total discontinuation 16%). There was no significant difference in the MTX dosage, the demographic and clinical features between the patients with and without adverse effects during MTX treatment.

Interestingly, toxicity was more common in patients with normal genotype than in those with both heterozygotes and homozygotes (p = 0.005 analysed by Fisher's exact test). Moreover, in multivariate analysis of variance the MTHFR genotype was the most important independent risk factor predisposing to MTX related toxicity (p = 0.042), compared with the other variables analysed—namely, age, sex, duration, and type of treatment (MTX alone or in combination with corticosteroids and/or other disease modifying anti-rheumatic drugs).

To our knowledge, this is the first study illustrating an inverse relationship between an MTHFR C677T variant and MTX related toxicity, in which the presence of toxicity was more common in patients with the normal 677CC genotype. In previous studies the presence of an MTHFR C677T polymorphism was associated with a higher incidence of MTX related toxicity in patients with rheumatoid arthritis and cancer, and also with an increased risk of discontinuing MTX treatment because of adverse events.² A study did not receive folate supplementation, or they received it after the emergence of toxicity. Interestingly, other studies did not support such a correlation.³ A possible explanation of our results, similar to the protective effect of the MTHFR C677T polymorphism in carcinogenesis,⁴ is that this polymorphism, in the presence of adequate folate supply, results in sustained ability of DNA synthesis and repair through increased synthesis of purines and thymidine, and subsequently in decreased MTX related toxicity.

In conclusion, our data suggest that a folate supply is critical among patients with autoimmune diseases and different MTHFR genotypes. When folic acid is given, subjects with MTHFR 677TT and C677T may be at reduced risk of MTX related toxicity, probably because of the sustained ability of DNA synthesis. This protective effect is absent in subjects with MTHFR 677CC and in subjects with MTHFR 677TT and 677TT receiving MTX without folate supply, as has been shown in previous studies. In addition, our results indicate the importance of genotyping to provide useful information for individualised treatment in patients with autoimmune diseases.

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Primary antiphospholipid syndrome: a unique presentation with multiple visceral aneurysms

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We present a unique case of a young woman with a proven primary type of antiphospholipid syndrome (APS) and multiple abdominal visceral aneurysms. Only one other case with such an association has been reported before to our knowledge. The presence of visceral aneurysms poses a therapeutic challenge because the anticoagulation treatment may be catastrophic in view of the risk of aneurysm rupture and abdominal bleeding.

A 38 year old woman was transferred from the department of obstetrics and gynaecology of the hospital, because of peripheral oedema. Two days earlier she had had a third trimester pregnancy loss. She had a history of four unexplained deaths of morphologically normal fetuses at the third trimester, during the past 10 years. She was the mother of a healthy 7 year old child. A diagnosis of primary APS was made based on clinical and serological criteria. Anticardiolipin IgG antibodies were present at a moderate level (48 GPL units; normal <19 GPL). There was no evidence of a concurrent systemic disease as documented in all detailed laboratory examinations performed for almost 1 year. Computed tomography of the abdomen disclosed multiple partially thrombosed and calcified visceral aneurysms affecting the splenic, hepatic, and both renal arteries, which were further documented with selective angiography (fig 1). The course of the patient’s disease was uneventful for 3 years, but progressive pulmonary, renal, and hepatic malfunction then started to develop. She progressively deteriorated and died from multiorgan failure. Postmortem examination confirmed the presence of the splachnic aneurysms without any evidence of rupture.

APS is one of the most important causes of hypercoagulability. About 50% of patients with APS do not have an associated systemic disease and are labelled as cases of primary APS. The association of APS and arterial aneurysms is controversial and poses a critical therapeutic dilemma. Lifelong anticoagulation remains the fundamental treatment for APS and may obviously be hazardous in the presence of multiple aneurysms. Although in most cases of secondary APS the presence of arterial aneurysms can be attributed to the underlying systemic disease, the pathogenesis of such aneurysms in primary APS—such as in our case—remains unclear.

Kong et al reported a case of a young man with systemic lupus erythematosus and secondary APS who presented with acute abdominal pain owing to a ruptured right hepatic artery aneurysm. He was also found to have aneurysms of the left hepatic artery and splenic artery on necropsy. The aetiology of these aneurysms according to the authors and based on histological examination of the aneurysmal wall, was found to be systemic lupus erythematosus vasculitis.

Dongola and Foord described a case of primary APS presenting with varied arterial abnormalities. These included the presence of a large number of micro- and macro-aneurysms of hepatic, renal, and mesenteric arteries. There was insufficient evidence to merit a concurrent diagnosis of polyarteritis nodosa or other associated systemic condition. The authors suggested that the arterial abnormalities in this patient might have been inherent to the syndrome itself and that APS can present protean vascular abnormalities, which represent a wide spectrum without associated vasculitis.

Our case is a further example of the unusual presentation of APS without any association with other syndromes, as shown by all laboratory examinations and documented by postmortem histological examination of the diseased arteries. Based on a literature review, we did anticoagulate the patient because there was serious concern about thromboembolic disease, despite the presence of multiple intra-abdominal aneurysms. We also followed all the other treatment protocols, including steroids and plasmapheresis, with the intention of provoking regression of the aneurysms. Such a regression was noted in a case of APS associated with polyarteritis nodosa, with a significant decrease in both the number and size of splachnic aneurysms after intensive treatment. In our case this treatment was unsuccessful because the postmortem examination showed the presence of the aneurysms, albeit without any evidence of aneurysm rupture or internal bleeding.

Despite the fact that the patient received all the appropriate supportive treatment, her disease progressed and she

Figure 1  Contrast enhanced computed tomography of the abdomen (A) shows large, partially thrombosed aneurysms of the splenic and hepatic arteries (arrows). Multiple splenic artery aneurysms are confirmed on selective angiography (B).
A family with diffuse idiopathic skeletal hyperostosis

C Gorman, A S M Jawad, I Chikanza

We report a family with diffuse idiopathic skeletal hyperostosis (DISH). The most striking occurrence was severe cervical disease without extensive dorsal involvement. From the tissue typing results of our two sibling patients, it appears less likely that, if there is a hereditary component, it is linked to HLA status. It remains to be seen whether this is a new disease entity or an unusual familial variant of DISH. We are unaware of a similar published report.

A 23 year old man was referred with a painful stiff neck of 3 years’ duration. On examination, all movements of his cervical spine were restricted. Other spinal movements were normal. Inflammatory markers were normal and HLA-B27 was negative. An x-ray examination of the sacroiliac joints, thoracic and lumbar spine were unremarkable. However, the cervical spine radiograph showed gross anterior osteophytosis (fig 1A).

This man’s 24 year old sister had been seen 7 years previously. She described a 6 year history of worsening neck pain and stiffness. On examination, movements of the cervical spine were severely limited in all directions, with mild limitation of the thoracic spine. An x-ray examination and inflammatory markers were normal and HLA-B27 was negative. Five years later, the clinical findings had scarcely changed. However, although the sacroiliac joints were still normal, there was now marked osteophytosis around the hip joints with gross osteophytosis and ankylosis of the cervical spine (fig 1B). Two years later, this advanced cervical pathology precipitated cervical myelopathy.

The father of these patients was first seen at 52 years of age despite having a “30 year history of ankylosing spondylitis”. He had a strong family history of the disease, with brother, sister, and mother affected. On examination, all spinal movements were markedly reduced. Movements of both hips were severely restricted and bilateral elbow fixed flexion deformities were present. Inflammatory markers were normal and HLA-B27 was negative. An x-ray examination showed normal sacroiliac joints, advanced osteophytosis and degeneration of the hip joints, and ankylosis of the cervical spine (fig 1C). His hip disease required prompt replacement surgery.

All these patients had radiological changes suggestive of DISH. Two of this patient’s siblings also had the disease, as do his other two offspring (they are receiving care at different hospitals). The first two patients described here were tissue typed: these siblings only shared alleles at DRB3 and the C locus, which occur frequently in the general population.

DISH is an ossifying, non-inflammatory, non-erosive enthesopathy favouring the dorsal spine but sparing the sacroiliac joints. By contrast, ankylosing spondylitis is an inflammatory condition with enthesopathies facing joints, always affecting the sacroiliac joints. DISH affects 3–6% of the population over 40 years of age and 11% aged over 70 years. It is twice as common in men and occurs more frequently in certain racial groups: it is common in Japanese and Pima Indians but rare in black and Asian races. Other causes of hyperostosis or bony excrescences include spondylitis deformans, ankylosing spondylitis, trauma, fluorosis, treatment with retinoids, ochronosis, acromegaly, hypoparathyroidism, and x-linked hypohosphataemic osteomalacia, but there was nothing in the history, physical examination, or the investigations to suggest that our three patients had any of those conditions.

In the cervical spine, ossification of the posterior longitudinal ligament (OPLL) is commonly seen. This phenomenon is often called “Japanese disease” owing to its predominance in the Japanese population. OPPL displays a strong genetic component with high concordance in twins and families. Various modes of inheritance have been suggested, including HLA linkage. In DISH, however, although there are racial differences, no strong familial tendency has been demonstrated. Neither is there a proven
HLA link, as found between HLA-B27 and the spondyloarthropathies. Although our patients were diagnosed as DISH, there are some atypical features. The most striking of these is severe cervical disease without extensive dorsal involvement. Forestier and Rotes-Querol in their classification criteria, considered involvement of at least three intervertebral bodies in the dorsal spine to be essential. However, Utsinger’s criteria do not include this as a necessary feature. One similar case has been described: a 71 year old patient presented with similar cervical findings and sparing of the dorsal spine and sacroiliac joints. Difficulty was found classifying the condition as either DISH or ankylosing spondylitis. Another unusual feature in our cases is the strong familial pattern. From the tissue typing results of our two sibling patients, it appears less likely that, if there is a hereditary component, it is linked to HLA status. It thus remains to be seen whether this is a new disease entity or an unusual familial variant of DISH.

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**REFERENCES**
gestation or later), and one patient had a premature birth (before the 34th week of gestation) due to severe pre-eclampsia. Platelet count was normal in all patients. Only one patient had a prolonged activated partial thromboplastin time. One hundred healthy donors with no relevant medical history comprised the control group.

aCL, anti-β2GPI, and aPS-PT were detected by enzyme linked immunosorbent assay (ELISA).1,2

aPL were present in 8/25 patients. Table 2 shows the distribution of aPL in patients and controls. aCL for IgG/IgM and aCL IgG were more frequently found in patients with scleroderma than in controls (32% vs 4%, p = 0.03, respectively). The prevalence of anti-β2GPI did not differ between patients and controls (8% vs 3% for IgG/IgM, 4% vs 2% for IgG, and 4% vs 1% for IgM).

Interestingly, patients with telangiectasia and pulmonary hypertension had IgM aPS-PT more frequently than those without (37.5% vs 0%, relative risk = 4.4 (2.0–9.5), p = 0.02 and 66.6% vs 4.5%, relative risk = 14.6 (1.8–116.9), p = 0.03, respectively). No associations were found between the other aPL analysed and clinical manifestations of scleroderma.

One patient with scleroderma who had had venous thrombosis also had IgG aCL at low titres. Of the two patients with a history of miscarriages (<10th week of gestation), one had IgG anti-β2GPI and the other IgM aPS-PT. None of the patients who had fetal death (n = 2) or prematurity (n = 1) had aPL.

Although the presence of all aPL was more common in patients with scleroderma than in healthy controls (32% vs 5%), the clinical manifestations of antiphospholipid syndrome were not frequently seen in these patients.

The prevalence of aCL in scleroderma has been reported to range from 0% to 41%.1 In this study, only one patient had a history of venous thrombosis and aCL at low titres, suggesting that this manifestation may have been aCL related.

Parodi et al described anti-β2GPI in 3/90 (3.3%) patients with scleroderma,2 whereas Schoenroth et al reported a prevalence of 8% when studying 26 patients with this disease.2 These studies are in agreement with our findings.

Although the prevalence of aPS-PT was low in our study, these antibodies were more frequently found in patients with telangiectasia and pulmonary hypertension, supporting the data from Hasegawa et al in their cohort of 112 patients with scleroderma.3 Overall, these findings suggest that aPS-PT may be a marker of vascular involvement in patients with scleroderma. However, as this is a very small study, further research is warranted to confirm or reject this hypothesis.

In summary, aPL are commonly found in patients with scleroderma but the “typical” clinical manifestations of antiphospholipid syndrome are not frequently seen in these patients.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Limited (n = 18)</th>
<th>Diffuse (n = 7)</th>
<th>All (n = 25)</th>
</tr>
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<tbody>
<tr>
<td>Calcification</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>17</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Oesophageal dysmotility</td>
<td>9</td>
<td>4</td>
<td>13</td>
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<tr>
<td>Sclerodactyly</td>
<td>12</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>11</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Intestinal lung disease</td>
<td>10</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac manifestations</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bowel disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All patients were attending the 2nd Chair of Rheumatology, Rheumatology Division and Centre for Systemic Rheumatic Diseases, Cagliari University Hospital, Cagliari, Italy.

Table 2

<table>
<thead>
<tr>
<th>Distribution of aPL in patients with scleroderma and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleroderma (n = 25)</td>
</tr>
<tr>
<td>aCL 8</td>
</tr>
<tr>
<td>IgG 4</td>
</tr>
<tr>
<td>IgM 2</td>
</tr>
<tr>
<td>Anti-β2GPI 2</td>
</tr>
<tr>
<td>IgG 1</td>
</tr>
<tr>
<td>IgM 1</td>
</tr>
<tr>
<td>aPS-PT 3</td>
</tr>
<tr>
<td>IgG 0</td>
</tr>
<tr>
<td>IgM 3</td>
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</table>

References

Remitting seronegative symmetrical synovitis with pitting oedema/polyarthalgia rheumatica after infection with Mycoplasma pneumoniae

M Matsuda, Y Shimojima, T Gono, W Ishii, K Kaneko, M Yazaki, S-I Ikeda

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) is similar to polyarthalgia rheumatica (PMR) in that it shows arthralgia attributable to tenosynovitis and muscle pain, occurring most commonly in the elderly, and shows a good response to corticosteroid treatment. The aetiologies of RS3PE and PMR are still unknown, but they are sometimes associated with neoplastic, other rheumatic, or infectious diseases.

Here, we report clinical findings in four patients with RS3PE or PMR, or both, after infection with Mycoplasma pneumoniae. Increases in inflammatory reactions were seen in all patients, and the final diagnoses were RS3PE alone in patients 1 and 4, RS3PE associated with PMR in patient 2, and PMR alone in patient 3 (Table 1). None of the patients had a headache or blurred vision suggestive of associated temporal arteritis. Recent infection with M pneumoniae was confirmed in all patients by the presence of IgM antibody to this agent in the serum and the results of serial serological studies with or without a positive cold agglutination test. Serum IgM levels were within the normal limits in all patients, and none showed positive results for serological tests for other infectious agents or autoantibodies such as rheumatoid factor or antinuclear antibody. All patients were treated successfully with oral prednisolone, but two relapsed during the tapering of this drug.

There are three possible characteristics of RS3PE/PMR after infection with M pneumoniae. The first is the presence of common cold-like symptoms preceding RS3PE/PMR. Two of the four patients showed common cold-like symptoms, and antibiotics were given to patient No 1 because chest radiography demonstrated bilateral pleural effusion due to active infection with M pneumoniae. The extremely high C reactive protein level with an almost normal erythrocyte sedimentation rate in patient 1 may have reflected previous infection with this agent.

The second characteristic is the frequent occurrence of relapse. RS3PE usually shows a good response to corticosteroid treatment, and is generally unlikely to relapse during tapering of drug treatment. However, relapse occurred soon after the start of tapering of oral prednisolone in two patients (Nos 1 (Fig 1) and 2) in the present study.

The third characteristic is a broad spectrum of clinical phenotype. Patients 1, 2, and 4 had oedema in the hands and feet, which is typical of RS3PE, while patient 3 had muscle pain alone, suggestive of PMR. Patient 2 was diagnosed as having RS3PE associated with PMR at the onset of disease, but at relapse the patient had PMR symptoms alone. A possible explanation for these findings is that RS3PE and PMR may be classifiable as the same disease entity with their symptoms of multiple tenosynovitis, and many transitional forms have clinical features of both disorders. The clinical phenotypes manifested after infection with M pneumoniae may be dependent on the host-disease relationship.

Several lines of evidence suggest that Mycoplasma species can cause rheumatic disorders. Previous exposure to Mycoplasma species is commonly confirmed by immunoblotting in patients with rheumatoid arthritis or juvenile rheumatoid arthritis, but polymerase chain reaction showed no detectable DNA of these agents in the synovial fluid or tissue. A prospective epidemiological study in Denmark indicated that the incidence of PMR varied in parallel with epidemics of M pneumoniae infection. Further studies in larger numbers of patients are necessary to clarify the pathogenetic mechanism of RS3PE/PMR after infection with this agent.

**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Onset age/sex</th>
<th>Diagnoses at onset</th>
<th>Preceding common cold-like symptoms</th>
<th>Laboratory tests at onset</th>
<th>Treatment at onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ESR* (mm/1st h)</td>
<td>CRP* (mg/l)</td>
</tr>
<tr>
<td>1</td>
<td>82/F</td>
<td>RS3PE</td>
<td>+</td>
<td>24</td>
<td>111</td>
</tr>
<tr>
<td>2</td>
<td>77/F</td>
<td>RS3PE and PMR</td>
<td>+</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>75/M</td>
<td>PMR</td>
<td>-</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>72/F</td>
<td>RS3PE</td>
<td>-</td>
<td>30</td>
<td>13</td>
</tr>
</tbody>
</table>

*Normal values: ESR 3–11 mm/1st h; CRP <1 mg/l.*

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatica; RS3PE, remitting seronegative symmetrical synovitis with pitting oedema.

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Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide

C Metzler, A C Arlt, W L Gross, J Brandt

Leflunomide (LEF) was introduced as a new disease modifying antirheumatic drug in 1998. Up to now hepatotoxicity, hypertension, and diarrhoea have been reported as adverse events. Peripheral neuropathy (PNP) has been described in eight patients with rheumatoid arthritis (RA) and psoriatic arthritis. In the postmarketing surveillance PNP does not appear as a side effect.
This first retrospective study aimed at evaluating whether LEEF might be associated with PNP in a large cohort of patients with inflammatory rheumatic diseases.

All inpatients of a primary rheumatology clinic with systemic rheumatic diseases and treatment with LEEF between August 1998 and May 2004 were retrospectively screened for a new onset of PNP. Patients with definite reasons for PNP—for example, active vasculitis or collagenosis, diabetes mellitus, lack of vitamins, alcohol abuse, and neoplasms, were excluded. PNP was screened clinically and confirmed by electrophysiological examination.

Seven hundred and sixty-five patients with LEEF treatment were identified. PNP was diagnosed in 106 (13.5%) patients. Ninety-five patients were excluded with diabetes (22 patients), malignancy with cytotoxic treatment (2 patients), vasculitis (67 patients), and connective tissue diseases (4 patients). None of the patients with PNP and systemic rheumatic diseases potentially associated with PNP had any history of neuropathy or any clinical or serological signs of disease activity at the time of the first manifestation of PNP and were, for example, in remission.

Eleven of 785 (1.4%) patients were identified as having PNP that was possibly related to LEEF (table 1). These 11 patients received LEEF in a dose of 20–50 mg/day by mouth daily for RA in six patients, Wegener’s granulomatosis in two, and for other inflammatory rheumatic diseases in three patients, respectively. PNP had occurred within a median of 6 months (range 2–48) after the start of LEEF. Electroneuography and electromyography showed that PNP related to LEEF had an acute or subacute symmetric pattern in all patients. There was evidence of a mostly axonal affection in seven patients and demyelinating changes in two. Patients with PNP induced by LEEF were followed up for a median of 12 months (range 2–45). In eight patients LEEF was stopped and, in addition, washed out in three of them. PNP improved in 1/8 (37.5%) patients when LEEF was stopped and remained stable in eight, independently of stopping or continuing treatment with LEEF.

This retrospective analysis supports an association between treatment with LEEF and the occurrence of PNP. Comparable data about the epidemiology of PNP are rare; in 1992 Walters et al described a prevalence of 2.9% in a cohort of 480 healthy controls. Whether there is a dose dependent neurotoxic effect of LEEF is unclear. One patient of our cohort established a PNP after an accidental intake of a higher dose LEEF (50 mg/day). In contrast with this experience, no increase of PNP was seen in two different studies in which 20 patients with Wegener’s granulomatosis were treated with 30–40 mg/day LEEF for 2 years and in a preliminary report of 11 patients with RA who received LEEF in a dosage of 40 mg for a mean period of 4.4 months.

The underlying pathogenetic mechanism is still unknown. When LEEF was first used for the treatment of RA the possibility that LEEF might induce vasculitis was discussed after a report of a new onset of secondary vasculitis in two patients with RA. In the meantime further safe and effective treatment of primary systemic vasculitides did not support this hypothesis. Thus, one might argue that LEEF was not effective enough to suppress a secondary vasculitis in these two cases. Interestingly, in three patients with RA and LEEF related PNP nerve biopsies were performed showing a predominant axonopathic process and vasculitis of the arterioles.

In conclusion, PNP is a new adverse event of LEEF. Therefore we recommend close neurological monitoring during treatment with LEEF. In suspect cases stopping and washing out of LEEF by cholestyramine should be considered.

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Vasculitis, antiphospholipid antibodies, and renal artery stenosis

S N Paul, S R Sangle, A N Bennett, M El-Hachmi, R Hangartner, G R Hughes, D P D’Cruz

Antiphospholipid antibodies (aPL) are considered to be non-pathogenic in patients with vasculitis. We present five patients with primary vasculitis who had aPL and renal artery stenosis (RAS); one of these patients had coexistent renal pathology due to primary vasculitis, and micro- and macrophagy due to renal manifestations of the antiphospholipid syndrome.

A 44 year old white smoker presented with sinusitis, haemoptysis, and arthritis. She was normotensive. A chest x ray demonstrated cavitation lesions. She was CANCA positive and fulfilled the American College of Rheumatology criteria for Wegener’s granulomatosis (WG).1 aPL were detected, although she lacked a history of thrombosis or pregnancy morbidity. Her serum C reactive protein level was raised at 100 mg/l. Clinical and serological remission was achieved with intravenous cyclophosphamide followed by maintenance methotrexate and corticosteroid treatment.

After discontinuing corticosteroids, she became hypertensive and her previously normal renal function deteriorated. Her serum creatinine rose to 154 mmol/l and she developed mild proteinuria (0.41 g/24 hours). Her cANCA titre rose to 40 with a rise in erythrocyte sedimentation rate to 28 mm/1st h. She remained aPL positive. Repeat echocardiography demonstrated mild mitral and tricuspid regurgitation, moderate aortic regurgitation with normal left ventricular function. Renal biopsy demonstrated crescentic focal and segmental proliferative glomerulonephritis with features of a thrombotic microangiopathy (figs 1A and B). She received further intravenous cyclophosphamide and corticosteroid, with symptomatic resolution and improvement in serum creatinine (122 mmol/l), but the mild proteinuria persisted.

At follow up, she had persistent hypertension (220/100 mm Hg) despite treatment with three antihypertensive drugs, including an angiotensin converting enzyme inhibitor, proteinuria, and rising serum creatinine; oral cyclophosphamide was started. Her proteinuria increased to 2.14 g/24 hours and her serum creatinine rose to over 200 mmol/l within a few weeks. Magnetic resonance angiography of her renal arteries demonstrated a stenotic stenosis of the right renal artery with post-stenotic dilatation (fig 1C) and a non-atheromatous aorta. After angioplasty (fig 1D) the patient’s renal function improved, with a serum creatinine of 76 mmol/l and 24 hour urinary protein of 1.45 g/24 hours. She was formally anticoagulated with warfarin.

Table 1 includes four other patients with primary vasculitis, aPL, persistent hypertension, and RAS.

Renal disease is not uncommon in WG, Churg–Strauss, and microscopic polyangiitis.3 Untreated it may lead to end stage renal failure. Hypertension seen in vasculitis may be secondary to corticosteroid treatment or renal disease.

Atherosclerosis is the major cause of RAS (>90%), with a minority of cases due to fibromuscular dysplasia.3 Hypertension is a recognised feature of antiphospholipid syndrome. Recently, a high prevalence of RAS (26%) was demonstrated in relatively young hypertensive patients with antiphospholipid syndrome.4 In our cohort, all the stenotic lesions were well defined and distal to the ostia, and the aortae showed no evidence of atherosclerosis.

We believe that RAS seen in our cohort may be associated with aPL. The relatively young age of our patients and the absence of atheromatous aortae on magnetic resonance angiography argues against the atherosclerotic type of RAS seen in elderly patients. A possible mechanism for the development of RAS in our cohort is thrombosis, accelerated atherosclerosis, and/or smooth muscle hypertrophy.5

Earlier reports have suggested that the presence of aPL in primary vasculitis is not pathogenic.6-9 There are no reports to date of vasculitis associated with RAS and aPL. However, there have been case reports of aneurysmal dilatation of the renal arteries and RAS in polyarteritis nodosa and Takayasu’s arteritis; none of our cohort had either of these diseases.

In summary, the presence of systemic vasculitis and aPL may not be as benign as previously thought. When faced with patients with primary vasculitis, aPL, and uncontrolled hypertension, the possibility of RAS should be considered.

A colour version of fig 1 can be seen at http://www.annrheumdis.com/supplemental


References

Table 1 Patients with primary vasculitis, aPL, persistent hypertension, and RAS

<table>
<thead>
<tr>
<th>Patient No, sex</th>
<th>Type of vasculitis, organ involvement, and treatment</th>
<th>ANCA</th>
<th>Renal artery stenosis history</th>
<th>aPL and thrombosis history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, female*</td>
<td>WG diagnosed age 44</td>
<td>cANCA</td>
<td>R RAS diagnosed 4 years after vasculitis</td>
<td>Positive lupus anticoagulant on more than two occasions</td>
</tr>
<tr>
<td></td>
<td>Respiratory, joint, renal</td>
<td></td>
<td></td>
<td>Cardiac valve lesions, renal thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide, corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2, male</td>
<td>Churg-Strauss diagnosed age 46</td>
<td>pANCA</td>
<td>L RAS diagnosed 18 years after vasculitis</td>
<td>Positive lupus anticoagulant on two occasions</td>
</tr>
<tr>
<td></td>
<td>Cerebral vasculitis, cardiomyopathy, asthma, sinusitis, necrotising glomerulonephritis</td>
<td></td>
<td></td>
<td>1 Cerebrovascular accident</td>
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<tr>
<td></td>
<td>Corticosteroids, azathioprine, methotrexate,</td>
<td></td>
<td></td>
<td>1 Deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3, female</td>
<td>WG diagnosed age 47</td>
<td>cANCA</td>
<td>Bilateral RAS and coeliac artery stenosis diagnosed 7 years after onset of vasculitis</td>
<td>Positive lupus anticoagulant and antiphospholipid antibodies on two occasions</td>
</tr>
<tr>
<td></td>
<td>Pulmonary haemorrhage, crescentic glomerulonephritis, peripheral neuropathy</td>
<td></td>
<td></td>
<td>Miscarriages, superficial thrombophlebitis</td>
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<td>Azathioprine, cyclophosphamide, co-trimoxazole</td>
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<td></td>
</tr>
<tr>
<td>4, male</td>
<td>WG diagnosed age 56</td>
<td>cANCA</td>
<td>L RAS, superior mesenteric artery stenosis diagnosed 4 years after onset of vasculitis</td>
<td>Lupus anticoagulant positive on two occasions</td>
</tr>
<tr>
<td></td>
<td>Pulmonary haemorrhage, epistaxis, and scleritis</td>
<td></td>
<td></td>
<td>No thromboses</td>
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<tr>
<td></td>
<td>Methotrexate, cyclophosphamide, prednisolone,</td>
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</tr>
<tr>
<td></td>
<td>co-trimoxazole</td>
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</tr>
<tr>
<td>5, female</td>
<td>Primary idiopathic systemic vasculitis diagnosed age 42</td>
<td>Not present</td>
<td>Bilateral RAS diagnosed 13 years after onset of vasculitis</td>
<td>Positive lupus anticoagulant on two occasions</td>
</tr>
<tr>
<td></td>
<td>Inflammatory arthropathy, coronary arteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azathioprine, methotrexate, prednisolone</td>
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*Described above.
Therapeutic interleukin (IL) 1 blockade normalises increased IL1β and decreased tumour necrosis factor α and IL10 production in blood mononuclear cells of a patient with CINCA syndrome

M Seitz, R K Kamgang, H U Simon, P M Villiger


Mutations in the cold-induced autoinflammatory syndrome 1 (CIA1) gene cause inherited chronic autoinflammatory disorders such as Muckle-Wells familial cold urticaria and chronic infantile neurological cutaneous and articular (CINCA) syndrome. Up regulation of interleukin (IL) 1β was recently reported in unstimulated monocytes obtained from a patient with CINCA syndrome, and active inflammatory disease resolved rapidly and completely during treatment with anakinra in patients with CINCA and with Muckle-Wells syndrome.

We report on a 47-year-old male patient with the CIA1 mutation T348M presenting classical clinical features of CINCA syndrome. The disease was refractory to conventional anti-inflammatory drugs and infliximab, but was successfully treated with daily subcutaneous injections of 100 mg of recombinant human IL1 receptor antagonist (anakinra, Kineret; Amgen, Cambridge, UK). Before and after therapeutic IL1 blockade, we assessed clinical and humoral inflammatory disease activity and cytokine release (IL1β, tumour necrosis factor α (TNFα), IL6, and IL10) in cell culture supernatants; R&D enzyme linked immunosorbent assay (ELISA) kits with lower detection limits of 3.9, 15.6, 3.13, and 7.8 pg/ml from Ficoll-isolated and either unstimulated or lipopolysaccharide (LPS; 100 ng/ml) stimulated peripheral blood mononuclear cells (PBMC; 1×10⁶/ml RPMI 1640 +5% fetal calf serum) after 48 hours of cell culture.

Cell-specific staining for monocytes was performed with mouse FITC-antihuman CD14 (eBioscience; San Diego, CA). Flow cytometry data were acquired only with propidium iodide negative cells on a FACSCalibur equipped with four lasers, and data were analysed using CellQuest software (BD Biosciences).

Concomitant symptomatic drug treatment was kept unchanged. Before anakinra treatment the patient showed typical clinical and serological signs of active inflammatory disease, including rash, polyarthritis of wrists and metacarpal joints, leucocytosis with neutrophilia, and a moderate acute phase response. After 2 days the rash completely vanished and synovitis and morning stiffness had markedly improved. After 3 weeks complete clinical remission with absence of cutaneous and articular symptoms was achieved. Raised C reactive protein levels and erythrocyte sedimentation rate normalised and leucocyte and platelet counts decreased, whereas monocyte numbers did not change and lymphocyte counts increased (table 1).

At the functional level we did observe an enormous IL1β release from monocytes after LPS stimulation before treatment. This dramatically and progressively declined upon treatment with anakinra. Surprisingly, the secretion of IL6 from activated PBMC was completely blocked, and similar to our previous finding in the same patient, we observed a completely deficient IL10 and in this case a deficient TNFα response of monocytes to LPS stimulation before treatment. Therapeutic IL1 blockade, however, restored both, spontaneous as well as LPS-induced TNFα and IL10 secretion.

Based on the pretreatment findings on stimulation of PBMC in this patient, and in addition to our previous

<table>
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<th>Measure</th>
<th>Baseline</th>
<th>3 Weeks</th>
<th>9 Weeks</th>
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<tr>
<td>C reactive protein (mg/l)</td>
<td>47</td>
<td>9</td>
<td>4</td>
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<tr>
<td>Erythrocyte sedimentation rate (mm/1 h)</td>
<td>40</td>
<td>3</td>
<td>8</td>
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<td>Haemoglobin (g/l)</td>
<td>10.9</td>
<td>12.5</td>
<td>11.6</td>
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<tr>
<td>Leucocyte count (10⁶/μl)</td>
<td>15.6</td>
<td>8.1</td>
<td>9.4</td>
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<td>Monocyte count (10⁶/μl)</td>
<td>0.47</td>
<td>0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>Lymphocyte count (10⁶/μl)</td>
<td>1.4</td>
<td>2.87</td>
<td>2.87</td>
</tr>
<tr>
<td>Platelet count (10⁶/μl)</td>
<td>528</td>
<td>403</td>
<td>419</td>
</tr>
<tr>
<td>CD14+ cells among PBMC (%)</td>
<td>1.28</td>
<td>1.35</td>
<td>1.15</td>
</tr>
<tr>
<td>Cytokine secretion by PBMC (pg/ml)</td>
<td>&lt;3.9</td>
<td>&lt;3.9</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>Spontaneous IL1β</td>
<td>8.53</td>
<td>2943</td>
<td>271</td>
</tr>
<tr>
<td>LPS-induced IL1β</td>
<td>&lt;3.13</td>
<td>&lt;3.13</td>
<td>&lt;3.13</td>
</tr>
<tr>
<td>Spontaneous IL6</td>
<td>1921</td>
<td>&lt;3.13</td>
<td>&lt;3.13</td>
</tr>
<tr>
<td>LPS-induced IL6</td>
<td>&lt;15.6</td>
<td>225</td>
<td>188</td>
</tr>
<tr>
<td>Spontaneous TNFα</td>
<td>7.8</td>
<td>162</td>
<td>170</td>
</tr>
<tr>
<td>LPS-induced TNFα</td>
<td>7.8</td>
<td>163</td>
<td>175</td>
</tr>
<tr>
<td>LPS-induced IL10</td>
<td>7.8</td>
<td>162</td>
<td>170</td>
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</table>
finding, we suggest that there is a defect of LPS responsiveness of monocytes to the induction of TNFα and IL10.

This case confirms the excellent response of CINCA syndrome to treatment with human IL1 receptor antagonist. Our results suggest that patients with this hereditary autoinflammatory disorder may exhibit a profound dysregulation of IL1 and TNFα synthesis. However, we cannot exclude the possibility that the inability to detect TNFα before application of IL1 receptor antagonist owed more to a rapid decay of TNFα rather than reduced production. As this dysregulation is reversed by treatment with IL1 receptor antagonist, one may argue that therapeutic inhibition of otherwise aberrant IL1β secretion results in a compensatory up regulation or less decay of TNFα to maintain the host’s capacity to react to microbial agents and other types of danger signals. Furthermore, the overall up regulation of the TNFα pathway by interaction at the IL1 pathway illustrates that the cytokine imbalance is not due to a defect, but rather to a dysregulation. Finally, our results provide an explanation for the reason why TNF blocking agents are ineffective in certain autoinflammatory diseases.

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Reversible posterior leucoencephalopathy in scleroderma
W L Poon, C C Mok

A 34 year old Chinese woman with limited scleroderma presented with rapid onset of mental confusion and generalised tonic-clonic seizures. Her blood pressure control had been unsatisfactory in the preceding 4 weeks despite the use of three anti-hypertensive agents, which included an angiotensin converting enzyme inhibitor. Malignant hypertension (blood pressure 240/140 mm Hg on admission) was evident, with typical fundoscopic abnormalities, microangiopathic haemolytic anaemia, and rapidly deteriorating renal function with acute oliguric renal failure (increase in serum creatinine from baseline of 86 to 495 μmol/l in 3 days). There was, however, no evidence of left ventricular failure. Treatment was given in the intensive care unit with infusions of labetalol (up to 150 mg/h) and iloprost (up to 10 μg/h), large doses of captopril (150 mg/day), and haemodialysis. An urgent magnetic resonance imaging (MRI) scan

Figure 1  (A) Axial T2 weighted and (B) coronal fluid attenuated inversion recovery (FLAIR) images showing bilateral abnormal hyperintensities in the white matter of the cerebellum, cortex, and subcortical white matter of the occipital lobes (long arrows), and in the brain stem (short arrows).
of the brain showed marked vasogenic oedema distributed symmetrically at the cortex, and subcortical white matter of the occipital lobes, the cerebellum, and the brain stem (fig 1). With control of hypertension and dialysis support, she gradually regained full consciousness without neurological deficits. A repeat MRI scan 2 weeks later demonstrated complete resolution of the lesions. The clinical picture was compatible with a reversible posterior leucoencephalopathy syndrome (RPLS).

RPLS is a clinical syndrome characterised by headache, seizures, visual disturbances, and confusion. The MRI finding is often characteristic, with abnormal T2 weighted hyperintensity affecting primarily the white matter of the territories of the posterior circulation.1 The cerebral cortex and the anterior circulation territories may also be affected, but usually to a lesser extent. RPLS has been described in an increasing number of medical conditions, including hypertensive encephalopathy, eclampsia, neurotoxicity related to calcineurin inhibitors, and uraemic encephalopathy. Reversible vasogenic oedema is the underlying pathology of the abnormal MRI signal intensities. The exact pathogenesis of RPLS remains elusive but a breakdown of the autoregulation of cerebral blood flow and endothelial dysfunction resulting in leakage of fluid into the interstitium has been postulated.

RPLS has been described in many rheumatic diseases, including systemic lupus erythematosus, systemic vasculitides, and the overlap syndromes.2,3 However, we believe that this is the first report of RPLS in adult patients with limited scleroderma. Prompt recognition and treatment of this condition is essential as it is potentially reversible.

Experimental infection with Plasmodium falciparum does not result in the induction of anticardiolipin antibodies in healthy volunteers

J Damoiseaux, A van der Ven, R Hermsen, D Telgt, M Roestenberg, J W Cohen Tervaert, R Sauerwein

References


Experimental infection with Plasmodium falciparum does not result in the induction of anticardiolipin antibodies in healthy volunteers

J Damoiseaux, A van der Ven, R Hermsen, D Telgt, M Roestenberg, J W Cohen Tervaert, R Sauerwein


Antiphospholipid antibodies (aPL), particularly lupus anticoagulant or anticardiolipin antibodies (aCL), are diagnostic markers for the antiphospholipid syndrome, which is characterised by venous or arterial thrombosis or obstetric complications, or both. APL may also occur in association with a multitude of infectious agents. Asherson and Cervera, while reviewing infection related aPL, mentioned malaria as one of the parasitic infections that has been associated with the presence of aPL.indeed, two independent papers have described the high prevalence of aPL in patients with malaria. Jakobsen et al described the induction of IgM, but not IgG aPL during acute Plasmodium falciparum infection of Sudanese adults. The aPL were reactive with cardiolipin, phosphatidylinositol, and phosphatidylcholine. Facer and Agiostratidou examined adult patients of diverse ethnicity with uncomplicated non-severe malaria. They showed that P falciparum and P vivax infections are associated with the appearance of raised plasma levels of IgM and IgG aPL, and aCL were raised in over 75% of the patients with malaria. Patients with P falciparum had high aPL IgG levels, exceeding the levels seen in positive controls. Because the observed association may lack a causal relation, we recently evaluated the induction of aPL in 10 healthy white volunteers upon infection with P falciparum.

Anopheles stephensi mosquitoes were infected with the chloroquine sensitive NF54 isolate of P falciparum at the insectary, as previously described. Sets of female mosquitoes were allowed to feed on the forearms for 10 minutes. Subsequent dissection was performed to confirm the presence of sporozoites in the mosquito salivary glands. If not present, the feed was repeated until successful. Volunteers were carefully monitored by assessing blood films twice daily. Upon microscopic detection of parasites, volunteers were immediately treated with a standard curative regimen of chloroquine.

Blood was sampled one day before infection and 1, 7, 10, 12, and 20 days after infection. IgM and IgG aCL were analysed by commercial enzyme linked immunosorbert assay (ELISA: Pharmacia Diagnostics, Freiburg, Germany) in a serum dilution of 1:100. Results showed that all volunteers were negative for both IgM and IgG aCL before infection and remained negative for these antibodies during follow up. Thus, acute P falciparum infection does not result in the induction of aCL.

Nevertheless, although there seems to be no causal relation between malaria and aCL, the coexistence of aPL may further complicate malarial infection. For instance, thrombocytopenia is often (~60%) seen in patients with malaria, and
immune-mediated mechanisms have been suggested.\textsuperscript{4, 7} Furthermore, in Gambian children with cerebral malaria the titres of aPL are significantly higher in severe than in mild malaria.\textsuperscript{3} However, a protective role of aPL has also been suggested. East African children with cerebral malaria had significantly lower titres of IgM anti-phosphatidylinositol antibodies than those with non-severe malaria.\textsuperscript{2} This is possibly explained by the neutralisation of the pathogenic properties of parasite derived phospholipid.\textsuperscript{4}

Whatever the pathogenic role of aPL, our present results indicate that acute \textit{P. falciparum} infection does not induce these antibodies in a white population. Whether aPL develop during chronic infections remains to be determined. Because genetic factors have been demonstrated to be associated with the prevalence of aPL\textsuperscript{9} it can be expected that people originating from malaria endemic areas are more prone to the induction of aPL. Therefore, analysis of aPL upon experimental infection with \textit{P. falciparum} in healthy volunteers from malaria endemic areas may further unravel the causal relation between malaria and aPL.

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Competing interest statement: None of the authors have any competing interest.

Ethics approval: This study was approved by the medical ethics committee of the University Medical Centre Nijmegen.

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Population based studies of biological antirheumatic drug use in southern Sweden: comparison with pharmaceutical sales

P Geborek, E Nitelius, S Noltorp, H Petri, L Jacobsson, L Larsson, T Saxne, I Leden

This study aimed at assessing the drug costs for biological treatments in a geographically defined area in southern Sweden (Scania province, population 1 145 090, November 2002), and at identifying any geographical differences and changes with time in the overall use of these compounds. Also, we wanted to investigate the completeness of the registry held by the South Swedish Arthritis Treatment Group (SSATG).\textsuperscript{1} During the study period no economic prescribing restrictions existed for these drugs in the region. The Swedish social security system covers all prescribed drug costs exceeding SEK 1800 (€170) a year to all patients in need, where need is based on their physician’s judgment. Thus, the use of biological antirheumatic treatment was limited only by restricted drug availability and capacity of the administration facilities. Medical practice was, however, under strong influence by guidelines from the Swedish Rheumatological Association.

SSATG data were used to explore annual and regional relations, assessing the current and previous use of biological agents, prescription costs, and patient’s diagnoses. The figures were adjusted according to the census population registry during 2000–03. Owing to legal constraints, which do not allow direct data linkage between SSATG and prescription databases, SSATG derived annual theoretical costs and sales of pharmaceutical agents to outpatients during the period 2000–03 (public domain) were broken down according to the patient’s district of residency as the unifying concept. To obtain an estimate of the costs per week of using the different drugs we assumed the annual drug dosage to be 2550 mg etanercept, 2100 mg infliximab, 1040 mg adalimumab, and 36 500 mg anakinra, respectively. Year-specific pharmacy unit drug costs were used. In 2002 the resulting costs were SEK 144 935 (1 SEK = 0.1€) for etanercept, SEK 108 539 for infliximab, SEK 143 377 for anakinra, and SEK 112 895 for adalimumab. The estimated yearly consumption of etanercept and infliximab was based on a previous detailed health economic study,\textsuperscript{7} whereas for anakinra and adalimumab we used the dosage recommended by the manufacturers. Registry data was checked against an assumed disease prevalence of 0.5% of the adult population.\textsuperscript{7}
Costs per head varied by a factor of 10 between residential districts, mostly because of low population numbers in some residential districts. However, when related to the five larger healthcare districts, twofold differences remained. The proportion of patients treated increased progressively and was about 14.9% of all patients with rheumatoid arthritis (RA) in 2003. The proportion of diagnoses other than RA increased from 13.1% to 22.7% during the study (Fig. 1). Pharmacy based and SSATG estimated cost ratios for all biological agents varied between 0.95 and 1.07 for the study years, but ratios for the individual drugs varied between 0.77 and 1.58. Concordance between pharmacy and SSATG cost figures increased with time (table 1), mostly explained by the increasing number of rheumatological centres joining the SSATG. The number of biological treatments started increased from 24 to 46 per 100 000 inhabitants between 2000 and 2003 and the number of biological treatments withdrawn increased from 4 to 20 per 100 000 inhabitants. The proportion of new biological treatments in patients previously treated with a biological drug increased from 4% to 44% between 2000 and 2003.

The regular overestimation of etanercept and underestimation of infliximab in SSATG costs suggests that the estimates have a systematic error. Several explanations can be offered, including annual pauses of longer than 1 week for etanercept, and prescription of infliximab for diagnoses other than those included in the SSATG registry. It can be estimated

![Figure 1. Total and drug related yearly biological drug costs (A) and number of patients treated with biological drugs related to the diagnosis (B) during 1999–2003 in Scania, derived from SSATG information.](https://www.annrheumdis.com/graphics/10.1136/ard.2004.032870)
(table 1) that the SSATG includes >90% of patients with arthritis currently treated with biological agents. This allows reliable continuous documentation of effects and potential side effects. Furthermore, a regional pharmacovigilance registry is also useful for assessing local differences in the use of the drugs and for evaluation of monitoring costs.

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REFERENCES

Anti-cyclic citrullinated peptide antibodies in patients with rheumatoid arthritis treated with anti-tumour necrosis factor agents
A S Russell, W P Maksymowycz, M de Silva

De Rycke et al pointed out the interesting discord between rheumatoid factor titre and the titre of anti-cyclic citrullinated peptide (anti-CCP) antibodies in their patients responding to infliximab plus methotrexate treatment.1

We have looked at 158 patients receiving either infliximab or etanercept plus methotrexate and treated for a slightly longer period over 1 year, all of whom, by definition, had responded with at least an ACR20, and in whom pretreatment serum samples were available.

We found essentially the same result for anti-CCP antibodies. Twenty four (15%) serum samples were negative at the outset, one of these became strongly positive in the serum specimen after 1 year. Of those who were strongly positive, one became negative; otherwise the titres remained relatively stable. Whether this in any way reflects the observation that the extra-articular features of rheumatoid arthritis—nodules, pulmonary disease, etc—do not seem to respond to these therapeutic agents might be a suggestion worth considering.

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