LETTERS

Cladribine in the treatment of systemic lupus erythematosus nephritis

Systemic lupus erythematosus (SLE) nephritis often requires treatment with cyclophosphamide, which carries the risk of major side effects including infection, ovarian failure and bladder malignancy. Therapeutic strategies that would specifically target lymphocytes are appealing. Following the first report of the use of the purine nucleoside analogue cladribine (2-chloro-2-deoxyadenosine), a selective lymphocyte depleting agent, in the treatment of lupus nephritis,1 we report our experience in two patients with severe renal involvement.

CASE 1
A 32 year old woman was diagnosed with SLE at age 28, with polyarthritis, photosensitive rash, subcutaneous nodules, fatigue and lymphopenia. ANA, anti-dsDNA, anti-Sm and anti-RNP antibodies were present. Various immunosuppressants and corticosteroids failed to maintain a sustained remission. Two and a half years after presentation, she developed haematuria and proteinuria and renal biopsy revealed WHO Class III lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone were subsequently reintroduced and creatinine has again fallen to 118 µmol/l.

Table 1 shows the results of investigations before and after cladribine infusions for both cases.

Table 1 Results of investigations before and after cladribine infusions

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First infusion</td>
<td>Second infusion</td>
<td>First infusion</td>
<td>Second infusion</td>
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<tr>
<td>Proteinuria</td>
<td>12.25 µg/dl</td>
<td>4.2 µg/dl</td>
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<td>12.4 µg/dl</td>
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<td>7.2 µg/dl</td>
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<tr>
<td>Serum creatinine</td>
<td>190 µmol/l</td>
<td>120 µmol/l</td>
<td>154 µmol/l</td>
<td>163 µmol/l</td>
<td>149 µmol/l</td>
<td>243 µmol/l</td>
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<tr>
<td>Anti-ds DNA</td>
<td>132 IU/ml</td>
<td>98 IU/ml</td>
<td>292 IU/ml</td>
<td>&gt;300 IU/ml</td>
<td>171 IU/ml</td>
<td>49 IU/ml</td>
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<tr>
<td>C3</td>
<td>0.51 g/l</td>
<td>0.72 g/l</td>
<td>0.51 g/l</td>
<td>0.60 g/l</td>
<td>0.39 g/l</td>
<td>0.60 g/l</td>
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<tr>
<td>C4</td>
<td>0.13 g/l</td>
<td>0.15 g/l</td>
<td>0.12 g/l</td>
<td>0.16 g/l</td>
<td>0.12 g/l</td>
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<tr>
<td>C3d</td>
<td>22 units/ml</td>
<td>23 units/ml</td>
<td>20 units/ml</td>
<td>13 units/ml</td>
<td>12 units/ml</td>
<td>12 units/ml</td>
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<tr>
<td>Urine analysis red cells, hyaline granular, cellular casts</td>
<td></td>
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Reference ranges: serum creatinine 50–100 µmol/l, anti-dsDNA: 50–300 IU/ml positive, >300 IU/ml strongly positive, C3: 0.63–1.19 g/l, C4: 0.11–0.43 g/l, C3d: up to 12 units/ml.


Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506)

Patients with chronic renal failure often develop musculoskeletal problems such as renal osteodystrophy and amyloid arthropathy, and in successful renal transplantation other complications may ensue, particularly avascular necrosis.1 Since the availability of immunosuppressive agents for rejection, there has been a decrease in musculoskeletal problems, however, new complications have been described such as a symmetrical bone pain syndrome and reflex sympathetic dystrophy syndrome (RSDS), some of them related to cyclosporin.2

Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporine A—that is, calcineurin phosphatase inhibition.3 We report on a patient treated with tacrolimus, who developed a leg bone pain syndrome, two months after kidney transplantation.

The patient was a 50 year old woman with severe hypertension, treated with atenolol (100 mg/day), verapamil (240 mg/day) and clonidine (0.150 mg/day). She developed chronic renal failure and was treated with peritoneal dialysis in 1995. In 1997 she underwent a kidney transplant from a cadaver and immunosuppressive treatment with tacrolimus (4 mg/day) and prednisone (15 mg/day) was started. Two months after transplantation she reported progressive bilateral symmetric pain in the knees. Because of pain and difficulty in walking she was readmitted to our unit. At this time, the patient was receiving tacrolimus (4 mg/day) and prednisone (5 mg/day). Clinical examination revealed pain on movement and tenderness over the bone and joint line, without swelling.

Figure 1 Bone scintigraphy, showing increased uptake in both knees.

or increased temperature. She had no signs of autonomic vasomotor disturbances and arterial mobility was normal. Examination of the remaining peripheral and axial joints was normal.

Blood tests showed creatinine levels of 1.3 mg/dl, calcium of 10.1 mg/dl, phosphate of 3.5 mg/dl and urate of 7.2 mg/dl. Other laboratory findings were normal. Patchy osteoporosis in the knees was seen radiographically. Bone scintigraphy showed intense uptake in both the oesophageal and vascular phases in the knees (fig 1). Calcitonin treatment was begun (three monthly cycles of 10 intramuscular units/day during 20 days) without clinical improvement. Because of the high serum concentrations of tacrolimus (15 µg/ml) and the ineffective calcitonin treatment, tacrolimus was reduced to 2 mg/day. Nine months after transplantation, she was free of symptoms and radiographs and tacrolimus concentration (9.1 µg/ml) were normal. Changes in plasma tacrolimus concentrations subsequent to the resolution of symptoms did not occur and the patient continued asymptomatic.

We describe a complication in a patient treated with tacrolimus after kidney transplantation that is similar to that described by other authors in transplanted patients treated with cyclosporin. Although the radiographic and bone scintigraphy findings suggested RSDS, the symptoms of this patient were not the classic features of this entity. The efficacy of corticosteroids in the treatment of uncompli- cated RSDS has been demonstrated,13 although in this patient with cyclosporin A is very rare, there are case reports described in the literature.14 To our knowledge, this is the first case of a renal transplant patient with pain in the lower limbs, related to tacrolimus treatment. Addi- tional case reports are needed to support this association.

Figure 1 Bone scintigraphy, showing increased uptake in both knees.

Spleen haemorrhagic infarction and hazards of anticoagulation in Wegener’s granulomatosis

In the largest cohort published to date, no splenic involvement is described in Wegener’s granulomatosis (WG).1 We report on two patients who required splenectomy for symptomatic splenic infarction in the course of WG.

CASE 1

A 42 year old man was admitted with an eight month history of arthritis and low grade dyspnoea. Examination showed an acutely ill patient with a 39°C fever, oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purura, neuritis, and black discoloration of some fingers and toes. The spleen was not palpable. Silent anterior myo- cardial infarction was diagnosed because of raised MB-CK levels and ST-segment increase with loss of R waves in leads V1, V2, V3 on electrocardiogram.1 Antineutrophil cyto- plasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen.1 No antiphospho- lipid antibody or coagulation protein abnormality could be disclosed. Treatment consisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparinate, diltiazem, dinitrosorbide and enalapril. His short-term course was uneventful. At day 14, the patient suddenly developed a severe haemorrhagic shock. Echotomography of the abdomen showed a splenic mass. At laparotomy, the spleen was almost disrupted by voluminous haematoma. Histological analysis of the spleen showed widespread necrotising vasculitis with haem- orrhagic infarction. After five years of follow up, the patient is in complete remission with oral corticosteroide treatment.

CASE 2

A 23 year old young man was admitted in August 1996 because of repeated otitis media, sinusitis, epistaxis, headache, arthralgia with fever and weight loss. Despite a short course of oral corticosteroids and antibiotics, his general condition worsened. Antiproteinase 3 c-ANCA were disclosed in serum. Chest computed tomography showed pulmonary nodules. Intranasal endoscopic biopsies demonstrated necrotising vasculitis with epithelioid and giant cells. Treatment included oral prednisone and intravenous cyclophos- phamide pulses. After a few days, serum creatine concentration abruptly increased to 198 µmol/l and urine analysis showed micro- scopic haematuria and proteinuria. High dose methylprednisolone pulses were then given, intravenous cyclophosphamide was changed to a 100 mg/day dose and the patient eventually achieved remission. In October 1996, abdomen computed tomogra- phy showed an intraspinal lesion that was consistent either with a splenic infarct or haem- orrhagic infarction (fig 1). The latter course was marked by a WG flare in January 1997, which was complicated with massive thrombosis of the left iliofemoral vein and the inferior vena cava. No thrombophilic disorder could be found. Intravenous heparin was added and anticoagulation with acenocoumarol were given. Because of persistent left hypocondrium ten- derness, splenectomy was performed in Sep- tember 1997. Histological examination showed splenic infarction with organised haem- orrhage and sequelae of vasculitis (fig 2).

COMMENT

Because they are vessels without collateral flow, occlusion of distal parenchymal splenic arteries leads invariably to splenic infarction. Of note, two of the three patients described by Wegener in 1936 had splenic involvement.1 The frequency of splenic involvement ranges from 50% to 100% of WG cases at necropsy.5,6 Histological changes frequen-
showed massive or multiple areas of splenic necrosis, associated to a variable extent with central arteritis, splenic trabeculitis, follicular arteriolitis, disseminated parenchymatous granulomata and capsulitis (fig 2). Patients with splenic infarction in WG usually remain asymptomatic. Prominent splenomegaly is rare. With computed tomography, focal splenic infarction appears as well defined, peripheral wedge shaped areas of low attenuation. In WG, the diffuse vasculitis process often results in massive hypodense lesions involving the spleen parenchyma (fig 1). A peripheral rim of enhancement may be seen, as for spleen abscess, haematoma and lymphoma. Splenectomy has been performed successfully in some patients.

In another case, a spontaneous splenic haemorrhage was ascribed to vasculitis in a patient who had severe WG that required haemodialysis.

In our two patients, microscopic study of the spleen also showed haemorrhagic infarction caused by specific WG related vasculitis process. A severe splenic haemorrhage occurred in patient 1, which was clearly related to both necrotising vasculitis and hypocoeagulable state. Anticoagulation was indicated for inaugural myocardial infarction in case 1 and deep venous thrombosis in case 2, in both cases during active WG flare. Splenectomy was required in both our cases.

Our data suggest that antithrombotic treatment entails a specific risk of bleeding complications in patients with WG vasculitis. When anticoagulation is necessary in WG patients, computed tomography of the abdomen should be systematically performed and, if splenic infarction is disclosed, splenectomy should be considered.

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Figure 1 Contrast enhanced upper abdominal computed tomography: large hypodense area with a peripheral rim of normally enhancing tissue.

Figure 2 Cut gross pathological section of spleen shows changes corresponding to those seen by computed tomography. Large firm yellow (white) area consistent with infarction was surrounded by dark peripheral zone of splenic parenchyma.

Letters, Matters arising

Amiodarone induced lupus

Lupus related to amiodarone has not previously been described. We report on a patient who developed drug induced lupus (DIL) in association with amiodarone treatment. To our knowledge, this is the first report of amiodarone induced lupus (CD ROM: Medline, USA National Library: 1966–98).

A 61 year old white woman was admitted because of two weeks of pleuritic chest pain, dyspnea on exertion, and non-productive cough. She had malaise, intermittent fever, arthralgia, and weight loss for more than six months. There was no history of Raynaud’s phenomenon, oral ulcers or photosensitivity. She had a six year history of arterial hypertension and atrial fibrillation treated with amiodarone, digital and amiodarone (200 mg once daily) for the past two years.

Physical examination disclosed malar rash, an aortic systolic murmur (grade II/VI), and hypovolemia in both pulmonary bases. Laboratory studies showed an erythrocyte sedimentation rate of 90 mm 1st h. Peripheral blood examination revealed a mild normochromic and normocytic anaemia (10 g/dl), normal white blood cells count (4000/µl), with lymphopenia (20 per cent), and normal platelet count (180 x 10⁶/µl). Coagulation tests were normal. All serum chemistries, including thyroid function tests, creatinine phosphokinase, immunoglobulins, complement levels, and urine analysis were within normal limits. Coombs’ tests were negative. Rheumatoid factor was 1:320. Circulating immune complexes (IgG-C1q) were positive. Antinuclear antibodies (ANAs) were positive at 1:640; anti-Ro, anti-La, anti-dsDNA, anti-Sm, anti-histone antibodies, antiphospholipid antibodies, cryoglobulins, C reactive protein, VDRL and Mantoux test were negative. Blood and urine cultures were negative. Electrocardiogram was within normal limits, and the two dimensional echocardiogram showed mild aortic stenosis. Chest radiography revealed bilateral pleural effusions, without fibrosis or cardiomegaly. Pleural fluid was exudative, with lymphocytic predominance, without cytological features for malignancy. Cultures of pleural fluid for bacteria, including for Mycobacterium tuberculosis, were negative. Bone scan with technetium-99m showed increase uptake in hands, elbows, and knees. The histopathological examination of biopsy specimens of the skin, including indirect immunofluorescence stain, muscle and temporal artery did not show abnormal features.

The amiodarone was stopped and the patient progressively improved. No corticosteroids were given. On the third week she developed a transient relapse, with fever, malaise and with evidence of unilateral pleural effusion. One year after no clinical, analytical or radiological findings were present, and three years later she still remained free of symptoms, and the ESR, complete blood count, and radiological data were normal. The titre of ANA decreased but remained weakly positive at 1:40.

It is estimated that 3–7% of all patients with systemic lupus erythematosus (SLE) might have DIL. Clinical features of SLE and DIL are similar but there are certain distinguishing characteristics between them: the
patients with DIL are usually older; the prevalence of men and women is similar and the presenting symptoms are usually mild, with the patient usually complaining of malaise, fever and arthralgia, with or without arthritis, while skin, central nervous system or renal involvement is rare. Pleuropneumonic disease is frequent and, as in classic SLE, anaemia and leucopenia may be present. Serum complement components are usually normal, ANAs are positive but anti-dsDNA and anti-Sm are negative, while anti-histones antibodies can be detected in most of patients.  

The pathogenic mechanisms proposed for DIL include: cross reaction between drug and the nucleic acid; hapten complex formation between drug and nucleic acid, or structural damage to the chromosomal DNA; action of drug as an adjuvant or immunostimulant, which, in concert with appropriate immune response genes, triggers polyclonal B/T cell activation; and interference with the complement pathway.  

The incidence of side effects associated with amiodarone ranges from 40% to 92% and, in most of cases, these side effects are consequence of its potential to be directly toxic to several organ systems. However, there is also some evidence of immunologically mediated phenomena related to amiodarone. A positive skin and basophil degranulation tests with amiodarone, secretion of leukocyte inhibitory factor, positive lymphoblastic transformation and circulation of a specific antibody of the IgG class have been described. Moreover, several studies suggest that various biological and immunological markers of “systemic” disease activity are present in patients taking this drug. Circulating immune complexes, ANAs, and non-specific increase in ESR and white blood cell count, sometimes with eosinophilia, are common findings.  

ANA titre is not uncommon in an elderly patient. However, spontaneous SLE in elderly people is not usual and DIL must always be considered in the differential diagnosis. This case, presenting with malaise, fever, arthralgia, circulating immune complexes, and autoantibodies strongly suggests an immunological underlying condition. Moreover, this patient meets four SLE criteria: malar rash, serositis, haematological disorders (lymphopenia), and positive ANA tests. Imputability criteria of amiodarone induced lupus are present on a semilogarithmic basis with classic features of DIL and on a chronological basis with disappearance of most of the symptoms after amiodarone withdrawal. The relapse could be explained because of the long elimination half time of the drug and, in consequence, the immune response might progress despite discontinuation of the treatment.

**Antinuclear antibodies in relapsing polychondritis**

The prevalence of antinuclear antibodies (ANA) in relapsing polychondritis (RP) has been recently reported by Zeuner et al to be as high as 66%, usually in a low titre with a speckled pattern. We report here on our experience of ANA testing in patients with RP.

The charts of 180 patients followed up in our institution fulfilling the criteria for RP proposed by Michet et al have been recently retrospectively reviewed with special focus on dermatological manifestations and their relation with myelodysplasia. This aim led us to exclude 36 patients because the association of RP with potentially confounding diseases, such as systemic lupus erythematosus (SLE) present in nine, mixed connective tissue disease (MCTD) in five, rheumatoid arthritis in three, Takayasu arteritis in three, polyarteritis nodosa in one, and not provided in 10. Among the 144 patients remaining, 111 have been tested for ANA by using either Hep-2 cells or liver sections as substrate, or both. Most patients had repeated ANA determinations, including initial testing before onset of corticosteroid treatment, and the higher titres were considered for analysis. Figure 1 shows the histogram of ANA positivity according to ANA titre.

**Figure 1** Prevalence of ANA in “pure” RP according to ANA titre.

**Notes**


There is no association between polymyalgia rheumatica and acute parvovirus B19 infection

Parvovirus B19 has been associated with a growing number of diseases. Besides the frequent manifestations such as erythema infectiosum (fifth disease) in persons with underlying haemolytic anaemia, hydrops fetalis in pregnant women and acute or chronic arthritis a range of rather rare diseases have been described in recent reports. Among them are case reports on persistent parvovirus B19 infection in immune incompetent people, encephalitis, myocarditis, systemic lupus erythematosus (reviewed by Anderson and Youden) and rheumatoid arthritis. Furthermore, parvovirus B19 has been suspected to play a part in the aetiology of polymyalgia rheumatica (PMR). Because of the acute onset of PMR and its systemic symptoms an infectious disease may be a relevant factor. Additionally, autoimmune processes have been demonstrated in both, PMR and parvovirus B19 infection. As the receptor for parvovirus B19, the P-blood group antigen (globoside), is also present on endothelial cells an interrelation between parvovirus B19 and giant cell arteritis or PMR may be possible. Parvovirus B19 can only replicate in erythroid precursor cells in human bone marrow, but it is known that infection of cells non-permissive for viral replication leads to an excess production of the viral non-structural protein (NS1) without production of capsid protein VP1. The NS1 protein is cytotoxic and able to induce apoptosis, it probably plays a part in the pathogenetic process of the parvovirus B19 induced tissue damage. This is confirmed by the fact that antibodies against NS1 of parvovirus B19 are preferentially produced during chronic or persistent parvovirus B19 infections, for example in parvovirus B19 associated chronic arthritis.

To test the hypothesis whether PMR is associated with acute parvovirus B19 infection, we tested the seroprevalence of IgG antibodies against the two structural proteins VP1 and VP2 and against the non-structural protein NS1 in 110 PMR patients (patients with giant cell arteritis excluded; mean (SD) age 67.0 (8.8) years, range: 48–77 and, for comparison, in 135 healthy controls of different ages. At the time point of blood sampling (median disease duration at the time point of blood sampling: 0.6 years, range: 0–7.3, mean (SEM): 1.4 (0.2) years), 35 patients had no corticosteroids and 75 patients received on average an 15.2 (1.8) mg prednisolone/day. Furthermore, we investigated the interrelation between age, symptoms or laboratory parameters and the presence of NS1 specific antibodies in healthy controls and patients with PMR. Non-parametric Kruskal-Wallis one way analysis was used to compare means of different subgroups. The significance level was p<0.05.

Subjects in the control group had various medical histories (at the time serum was collected).

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2 Vo 120
Neutrophil chemotaxis in Behçet’s syndrome

It has been suggested that the marked cellular inflammatory response, which characterises Behçet’s syndrome (BS), may be attributable to increased neutrophil locomotion. However, others disagree. We have re-evaluated chemotaxis of polymorphonuclear leucocytes (PMNs) in BS among a greater number of patients in a controlled setting.

Fifty four male BS patients, nine male patients with ankylosing spondylitis, eight with psoriasis and 37 male healthy controls were studied with 28 female patients with BS and 16 healthy female controls. Behçet patients with severe disease were those with active major vessel and ocular involvement.

We measured chemotaxis with the “under the agarose method”. The measurements were masked with the assessors not knowing the diagnoses. An inverted microscope fitted with an ocular micrometre disc to measure the migration of neutrophils from middle wells to outer (chemotaxis) and inner wells (chemokinaxis) was used. Zymosan activated sera (patients or controls) were used as a source of C5a. Results were expressed as micrometre square (1 mm² = 8 squares). Additionally the plates were evaluated macroscopically for observation of the migration between neutrophil wells.

Tables 1 and 2 show the results. There were no significant differences between the chemotactic indices of the various groups of patients and controls studied of either sex. Maximal chemotaxis rates in the groups varied from 67% to 100%.

The Boydon millipore filter system has extensively been used for chemotaxis experiments. The agarose method is simple and cheap. This method can preferentially be used to differentiate chemokinesis from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS and we recognise that some of the confusion in the literature about neutrophil activity might be related to this. Thus we analysed our data separately for either sex. Although there was a tendency for male patients with severe disease to have higher C5a. Results were expressed as micrometre square (1 mm² = 8 squares). Additionally, the plates were evaluated macroscopically for observation of the migration between neutrophil wells.

The agarose method is simple and cheap. This method can preferentially be used to differentiate chemokinesis from chemotactic migration.

Table 1 Chemotactic indices in men*

<table>
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<tr>
<th>Groups</th>
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<th>Mean (SD)</th>
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<td>Severe Behçet’s</td>
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<td>11.3 (12.1)</td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>9</td>
<td>5.9 (7.1)</td>
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<tr>
<td>Psoriasis</td>
<td>8</td>
<td>10.8 (11.0)</td>
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<tr>
<td>Healthy controls</td>
<td>37</td>
<td>10.0 (10.3)</td>
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* Kruskal-Wallis one way analysis of variance, corrected for ties: $\chi^2 = 2.1381, \text{DF} = 4, p = 0.55$

Table 2 Chemotactic indices in women*

<table>
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<td>7.2 (8.2)</td>
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<tr>
<td>Healthy controls</td>
<td>16</td>
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*Ezra and colleagues observed decreased chemotaxis in BS. Fordham et al, on the other hand reported increased chemotaxis, but normal random migration. While Wilkinson, similar to our experience, observed normal chemotaxis in BS, more recently Carlotto et al reported augmented chemotaxis especially in the active phases of the disease. Finally, Ben Ezra et al, among a group of Behçet patients with uveitis could demonstrate increased chemotactic activity among a few of these patients, compared with that observed among patients with other forms of uveitis. They concluded that increased chemotactic activity was not a regular feature of ocular BS (personal communication).

In vivo assays do not differentiate chemotaxis from chemokinesis. In the Carlotto study clinically active Behçet patients demonstrated increased chemotaxis to sera by Sen’s modified in vivo assay. Others had found hyperchemotaxis to be present in patients with Behçet’s disease. In our experiments we observed maximal chemotaxis (5 mm) frequently, however, we did not find any significant differences in chemotactic indices between diseased and healthy subjects.

An interesting aspect of our study was the migration between neutrophil wells that was observed in many of the Petri dishes. This was observed even though we had not used cellular materials as chemotactic agents. Presumably the gravity of the cellular materials overcame the chemical gradient of zymosan activated sera in some Petri dishes. Because of the observed migration between neutrophil wells, we suggest that there should be only one “triple well rank” in a Petri dish. On the other hand our method of preincubation of the whole blood for 45 minutes at 37°C before harvesting the PMNs (intended for better viability) might have been responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

The critical differences in making sense of the literature on patients with lupus involving the central nervous system are re-emphasised in the paper by Rood et al. The authors, who do not agree, make the kind of claim they have made? The authors suggest that CNS lupus is attributable to either antiphospholipid antibody related thrombotic events, or “immune mediated” disease. This division is artificial. There is a considerable literature on CNS lupus that proposes that a wide variety of immunopathogenic mechanisms may be responsible in individual cases. These mechanisms include thrombotic effects, which may be linked to antiphospholipid antibodies, a true vasculitis, a cross reaction between antibodies that recognise the lymphocyte surface targets and neurologic antigens, and antibodies to a wide variety of neurological targets. A considerably larger number of patients will have to be studied before any claims of links to an IL10 polymorphism or any of the other mechanisms.

Neuropsychiatric systemic lupus erythematosus

The considerable difficulties in making sense of the literature on patients with lupus undergoing isolated neurological disability is emphasised in the paper by Rood et al. The authors, who do not agree, make the kind of claim they have made? The authors suggest that CNS lupus is attributable to either antiphospholipid antibody related thrombotic events, or “immune mediated” disease. This division is artificial. There is a considerable literature on CNS lupus that proposes that a wide variety of immunopathogenic mechanisms may be responsible in individual cases. These mechanisms include thrombotic effects, which may be linked to antiphospholipid antibodies, a true vasculitis, a cross reaction between antibodies that recognise the lymphocyte surface targets and neurologic antigens, and antibodies to a wide variety of neurological targets. A considerably larger number of patients will have to be studied before any claims of links to an IL10 polymorphism or any of the other mechanisms.

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compared with controls in their study, we suspect that the difference in IL10 production is not attributable to functional differences between patients with SLE and controls in terms of the IL10 SNP alleles frequencies. Differences have been described with respect to microsatellites and one awaits confirmation from other populations or family studies. To our knowledge, a difference in IL10 production between patients with neuropsychiatric disease SLE and non-neuropsychiatric disease SLE has not been described. The described association would be biologically meaningless if IL10 production is similar between these two groups.

The authors suggest that the -1082A allele is associated with a higher innate IL10 production, however, they appear to ignore the only published study to date that showed that the A allele was associated with lower IL10 production. In addition we have confirmed that the A allele is associated with lower IL10 production in transient transfection studies and the ATA/ATA genotype is associated with lower IL10 production in whole blood culture. The increase in the A allele is mainly accounted for by an increase in the ATA haplotype in their neuropsychiatric disease patients and therefore they are described with a lower than normal IL10 producing haplotype, not a high IL10 producing haplotype. One interpretation of this would be that patients with neuropsychiatric disease symptoms are unable to adequately control inflammation from a variety of different pathological mechanisms because of low IL10 production.

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The increase in the A allele has been found to occur in the sense that CNS lupus is associated with a higher innate IL10 production. Because of the retrospective character of our SLE patients as a whole was similar to or lower than the control group stating that -1082 A is associated with high IL10 production and the pathogenesis of neuropsychiatric disease SLE. Isenberg et al have referred to another group stating that -1082 A is associated with a lower in vitro IL10 production and they interpret our results with this finding in mind. In conclusion, we do not know the relevance of the IL10 promoter in the in vivo regulation of IL10 production and therefore both explanations are equally speculative.

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Letters, Matters arising

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translation may occur. This compares with the iron regulated pathway of ferritin synthesis in haemachromatosis and iron overload syndromes.

A comparative study of diagnostic criteria in AOSD by Mason et al suggest the Yamaguchi criteria are superior to the others tested, including Cush et al quoted by Knight and Symmons. However, none of the criteria to aid diagnosis make use of serum ferritin measurement despite the claims for its use in the literature and acceptance in clinical practice. Although undoubtedly useful if very high, it is not clear what the relevance of a normal value in AOSD is, in a case satisfying clinical diagnostic criteria (although we have never seen such a case). In rare diseases such as AOSD, it is difficult to assess and evaluate diagnostic criteria and calculate sensitivity and specificity of possible disease markers. If serum were stored on this patient it would be interesting to know the serum ferritin measurement and how, if at all, it would have affected this patient’s management.

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Authors’ reply

We thank Drs Quinn and Gough for their interest in our paper. Our patient did have his serum ferritin measured in 1992. It was 197 µg/l (normal range 15–200). This was therefore a situation in which the patient satisfied clinical diagnostic criteria for adult onset Still’s disease (AOSD) but had a normal ferritin concentration. As the authors point out, had the ferritin concentration been high, this would have helped to confirm the diagnosis but given that it was in the normal range, it could not actually be used to refute the diagnosis. It was always felt that this patient’s disease was not typical of AOSD and the various physicians who looked after the patient were always willing to consider alternatives. However, it is difficult, even with the benefit of hindsight, to conclude that Whipple’s disease could have been diagnosed earlier. Although the normal serum ferritin was not in keeping with the diagnosis of AOSD it did not point towards any other diagnosis in particular.

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Ear, ear, what’s going on in Norfolk?

Having recently started work in the rheumatology department of the Norfolk and Norwich Hospital I read with great interest the article on Hug(h)e(s’) ears: an unusual presentation of antiphospholipid syndrome. Ann Rheum Dis 1999;58:65–6.

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Authors’ reply

We note with interest the report from Dr Gaffney. While the coincidence is indeed curious, these cases do suggest possible mechanisms for activation of thrombosis. The external ear is characterised particularly by a lower average temperature than core body temperature, and by its susceptibility to trauma and pressure effects. In our case, cryoglobulins were not identified, and no comment in this regard is made by the authors. There is no specific reference to any aural trauma, though presumably, as in our case, it is difficult to assess what pressure was exerted on the external ear during sleep. It is plausible that such pressure causes a degree of blood stasis, which together with inadequate anticoagulation, resulted in thrombosis. Such speculation may be interesting, but it is this latter point that deserves emphasis—patients with antiphospholipid syndrome who have had thrombi will do so again, potentially with serious consequences, if the INR is not scrupulously maintained above 3.0, a message that must be spread widely: “Friends, Norfolk countrymen, lend me your ears!”

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Spleen haemorrhagic infarction and hazards of anticoagulation in Wegener's granulomatosis

THOMAS PAPO, DU LE THI HUONG, JEAN-CHARLES PIETTE, MARC ANDRE, OLIVIER AUMAITRE, FREDERIC CHARLOTTE and JEAN-LOUIS KEMENY

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