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 showed progression to Class IV lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone was subsequently reintroduced and creatinine 40 mg/day proved ineffective as creatinine rose from 149 to 243 µmol/l in two months. She also developed a perianal herpes simplex infection but drug was otherwise well tolerated. Pulse intravenous cyclophosphamide and methyprednisolone 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.

In the initial study by Davis et al., three of seven patients treated with continuous cladribine infusion for a week responded completely and renal failure did not deteriorate in any of the seven patients. Our limited experience suggests that cladribine may be effective in other manifestations of SLE (that is, cutaneous vasculitis), but it does not seem to have a consistent effect in severe nephritis. Good tolerability of the drug was confirmed and although herpes simplex infections occurred in both patients the role of corticosteroids cannot be ignored.

Further studies are required to establish the position of cladribine in the treatment of SLE especially in the presence of other lymphocyte depleting agents such as mycophenolate mofetil, which is reported to be effective in lupus nephritis,2 even in cases refractory to cyclophosphamide.

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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,3 and in successful renal transplantation other complications may ensue, particularly avascular necrosis.4 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.5,6 Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporin A—that is, calcineurin phosphatase inhibition.7 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, treated with tacrolimus, who developed a leg bone pain syndrome, two months after kidney transplantation.

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

Table 1 Results of investigations before and after cladribine infusions

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>First infusion</th>
<th>Second infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>12.25 ± 24 h</td>
<td>4.2 ± 24 h</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>190 µmol/l</td>
<td>120 µmol/l</td>
</tr>
<tr>
<td>Anti-ds DNA</td>
<td>132 IU/ml</td>
<td>292 IU/ml</td>
</tr>
<tr>
<td>C3</td>
<td>0.51 g/l</td>
<td>0.72 g/l</td>
</tr>
<tr>
<td>C4</td>
<td>0.13 g/l</td>
<td>0.15 g/l</td>
</tr>
<tr>
<td>C3d</td>
<td>22 units/ml</td>
<td>23 units/ml</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>red cells, hyalurangranular, cellular casts</td>
<td>red cells, some casts</td>
</tr>
</tbody>
</table>

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

ors (albeit of the dihydropyridine type) can improve the bone pain syndrome. In the largest cohort published to date, no association was found between cyclosporin A and bone pain syndrome in transplant patients. The inhibition of T lymphocyte activation by tacrolimus (FK506). Wakisaka S, Sakane T. In vivo mechanisms for the inhibition of T lymphocyte activation by cyclosporin A in a renal transplant patient. Clin Exp Immunol 1994; 97:53–6. 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 osseous 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 uncomplicated RSDS has been demonstrated,2 although it is possible that corticosteroids might have a protective role against a full RSDS development, as she was treated with high doses of prednisone after the renal transplantation.

The early onset of symptoms after the administration of the drug and the clinical improvement after the reduction of the immunosuppressant dose, are features that support a possible relation between tacrolimus and the leg bone pain syndrome. The patient had high plasma tacrolimus concentrations at the onset of the clinical symptoms and the improvement appeared only when the drug doses went down. Although recurrence of knee symptoms with an increase in tacrolimus dose would be much stronger proof of this association, it is not ethically justifiable. Furthermore, she was treated with verapamil in addition to other drugs for controlling hypertension. Verapamil might have played a part in a possible increased risk for this clinical complication, because it decreases tacrolimus clearance.3 However, there are reports that calcium channel blockers would not significantly alter plasma tacrolimus levels.

**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). 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 lower limb dysaesthesia. Examination showed an acutely ill patient with a 39°C fever, oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purpura, 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. Antineutrophil cytoplasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen. No antiphospholipid antibody or coagulation abnormality could be disclosed. Treatment consisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparinate, diltiazem, dextrinosorbide 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 haemorrhagic infarction. After five years of follow up, the patient is in complete remission with oral corticosteroid 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 cyclophosphamide pulses. After a few days, serum creatinine concentrations abruptly increased to 198 µmol/l and urine analysis showed microscopic haematuria and proteinuria. High dose methylprednisolone pulses were then given, intravenous cyclophosphamide was changed to 100 mg daily and the patient eventually achieved remission. In October 1996, abdomen computed tomography showed an intrasplenic lesion that was consistent either with a splenic infarct or haematoma (fig 1). The later 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 during a 10 day period and short duration anticoagulation with acenocoumarol were given. Because of persistent left hydrocoele tendon tenderness, splenectomy was performed in September 1997. Histological examination showed splenic infarction with organised haematoma and sequelae of vasculitis (fig 2).

**COMMENT**

Because they are vessels without collateral flow, occlusion of distal parenchymal splenic arteries leads invariably to necrosis. Of note, two of the three patients described by Wegener in 1936 had splenomegaly.7 The frequency of splenomegaly ranges from 50% to 100% of WG cases at necropsy.8 Histological data frequently

![Figure 1: Bone scintigraphy, showing increased uptake in both knees.](image-url)


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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: Medicine, USA National Library: 1966–98).

A 24 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 twice times daily) for the past six months.

Physical examination disclosed malar rash, an aortic systolic murmur (grade II/VI), and hyperventilation in both pulmonary bases. Laboratory studies showed an erythrocyte sedimentation rate of 90 mm 1st h. Peripheral blood examination revealed a mild normocytic and normochromic anaemia (10 g/dl), normal white blood cells count (4000/µl), with lymphopenia (20 per cent), and normal platelets count (180 000/µl). Coombs 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 tests were negative.

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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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. Pleuropulmonary 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 reactivity 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 93% and, in most 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 leucocyte 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.

Low 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 disorder (lymphopenia), and positive ANAs test. Imputability criteria of amiodarone disorder (lymphopenia), and positive ANAs titre. Imputability criteria of amiodarone-induced hypersensitivity pneumonitis. Evidence of an immunologically mediated mechanism. Chest 1987;94:625–30.


**Antinuclear antibodies in relapsing polychondritis**

The prevalence of antinuclear antibodies (ANA) in relapsing polychondritis (RP) to 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 reported 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, mesentric panniculitis in three, spondyloarthropathy in two, Crohn’s disease in two, psoriasis in two, or Lichten planus in two. 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.

ANA were either absent or present in low titres in a majority of patients (73% and 18%, respectively). “Significant” titres—that is, titre > 1/100 ANA—were demonstrated in only 10 of 111 patients (9%). The pattern of fluorescence was as follows: homogeneous in five, homogeneous and speckled in two, speckled and nucleolar in one, perinuclear and nucleolar in one, and not provided in one. Among those 10 patients, five had clinical or ophthalmological features, or both, suggestive of an associated Sjögren’s syndrome—agrees with the negative results of ANA in four of their 18 patients tested (22%), and noted 3 of 23 (13%) ANA positivity in a literature review. Data regarding ANA were not provided in the large series of patients with RP followed up at the Mayo Clinic. The low prevalence of ANA observed in our cases with “pure” RP—that is, RP not associated with another connective tissue disorder except for a possible Sjögren’s syndrome—agrees with the negative results of tests for IgG antinuclear antibodies commonly reported by our group in this condition.

We conclude that: (a) the prevalence of ANA observed in RP is low and, (b) as suggested by other authors, the finding of a significant titre of ANA in a patient with RP strongly suggests the presence of an associated disorder, such as SLE, MCTD, Sjögren’s syndrome or acquired myelodysplasia.

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

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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, parvovirus B19 has been described in persons with underlying haemolytic anaemia, hydrops fetalis in pregnant women and acute or chronic arthritis. However, other symptoms and parameters of inflammation such as crythrocyte sedimentation rate were not associated with the presence of NS1 IgG. Furthermore, disease related immune mediators such as interleukin 6 or soluble ELAM were lower in patients with as compared with patients without NS1 IgG. No significant differences were found with respect to erythrocyte sedimentation rate, C reactive protein, tumour necrosis factor, interleukin 2, and interleukin 1β.

In view of these data, there was a positive association between NS1 and arthralgia. However, other symptoms and parameters of inflammation such as crythrocyte sedimentation rate were not associated with the presence of NS1 IgG. Furthermore, disease related immune mediators such as interleukin 6 or soluble ELAM were lower in patients with as compared with patients without NS1 IgG. As a positive NS1 IgG indicates an active infection, an acute parvovirus B19 infection does not seem to be a pathogenetic factor in our patients with PMR.

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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.1,2 However, others disagree.3

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/or eye involvement.

We measured chemotaxis with the “under the agarose method”.4 The measurements were masked with the assessors not knowing the diagnoses. An inverted microscope fitted with an ocular micrometer disc to measure the migration of neutrophils from middle wells to outer (chemotaxis) and inner wells (chemokinesis) was used. Zymosan activated sera (patients or controls) were used as a source of C5a. Results were expressed as micrometre square (1 mm=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 Boyden millipore filter system has extensively been used for chemotaxis experiments.5 The agarose method is simple and cheap. This method can be preferred to be used to differentiate chemokinesis from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS6 and we recently reported 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 chemotactic indices this was not statistically significant (p=0.62). We did not study any diseased controls for female patients with BS.

Abdulla and Lehner7 observed decreased chemotaxis in BS. Fordham et al.,8 on the other hand reported increased chemotaxis, but normal random migration. While Wilkinson,9 similar to our experience, observed normal chemotaxis in BS, more recently Carletto et al.3 have reported increased chemotaxis in BS, among a group of Behçet patients.

In vivo assays do not differentiate chemotaxis from chemokinesis. In the Carletto study clinically active Behçet patients demonstrated increased chemotaxis to sera by Senn’s modified in vivo assay. Others had found hyperchemotaxis to might have been responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

<p>| Table 2 Chemotactic indices in women* |</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behçet’s</td>
<td>28</td>
<td>7.2 (8.2)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>16</td>
<td>10.1 (10.2)</td>
</tr>
<tr>
<td>*p&lt;0.05</td>
<td></td>
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</tr>
</tbody>
</table>

not a regular feature of ocular BS (personal communication).

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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.


**Neuropsychiatric systemic lupus erythematosus**

The considerable difficulties 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 to be fair take a sensibly cautious approach to their results, nevertheless seek to persuade us that the IL10 locus is associated with neuropsychiatric lupus on the basis of a historical case notes review of 42 hospitalised patients with neuropsychiatric disease, compared with 50 who lack such involvement.

Their conclusion needs to be treated with caution. Does it make sense to lump together 42 highly diverse patients and 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 neuroantigens, 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 promoter haplotype can be truly convincing.

We agree with the authors that patients with SLE have a higher innate production of IL10 than controls. However, as there is no significant difference in the frequency of the IL10 promoter single nucleotide polymorphism (SNP), in SLE patients, when
Mediated and tromboembolic disease is too rigid, and both conditions in CNS lupus 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 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 describing an association with a low 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.


The authors argue that the dichotomy of the pathogenesis of CNS lupus in "immune mediated" and tromboembolic disease is too rigid, and both conditions 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.

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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.

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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Antinuclear antibodies in relapsing polychondritis

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Ann Rheum Dis 1999 58: 656-657
doi: 10.1136/ard.58.10.656

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