LETTERS

A successful renal transplantation in Behcet’s syndrome

Renal involvement is not frequent in Behcet’s syndrome (BS) and consists of occasional reports of patients suffering from glomerulonephritis,1 IgA nephropathy2 and renal amyloidosis.3 We present the successful outcome of a renal transplantation in a patient who had end stage renal failure secondary to glomerulonephritis. To our knowledge, this is the first patient with BS to receive an organ transplantation.

The detailed history of this patient at the time of the diagnosis of glomerulonephritis was the subject of a case report in 1991.1 In brief, she was 21 years old when she developed recurrent oral and genital ulcers, bilateral uveitis, erythema nodosum, folliculitis, and intermittent arthritis of the knees. Two years later, she was referred to our centre for further evaluation of eye symptoms. She had no active mucocutaneous lesions at that time, the pathergy reaction was positive and she carried HLA B5. It was decided to prescribe only local drops for her mild eye involvement. Three months later she experienced two ocular episodes resulting in a sharp decline of visual acuity and azathioprine 2.5 mg/kg/day was prescribed. Two weeks later she was admitted to the hospital because of microscopic haematuria. She was ANA negative, the anti-DNA and serum complement levels were within normal range. Her glomerular filtration rate was 67 ml/min. An open renal biopsy showed diffuse proliferative glomerulonephritis and weak focal segmental positivity of IgA and IgM. She was treated with three boluses of 1 g methylprednisolone and was discharged prescribed azathioprine 150 mg/day, aspirin 300 mg/day and prednisone 30 mg/day. She was well except for occasional mucocutaneous symptoms and a mild local episode during the next four years. However her renal function deteriorated progressively despite uninterrupted treatment with azathioprine and changing doses of prednisone and she was put on regular haemodialysis two years later. Her glomerular filtration rate was 7 ml/min. A graft biopsy performed at that time showed diffuse proliferative glomerulonephritis.

A successful renal transplantation was treated successfully with pulsed corticosteroids, azathioprine, cyclosporin A and methylprednisolone. In lymphocyte phe- notyping in patients with BS and healthy controls.

We studied 29 patients (27 women, two men) 16 limited, 12 diffuse and one overlap who fulfilled preliminary criteria for classification of SSc.3 Anti-nuclear antibody was positive in 25 (86.2%) and anti-Scl70 antibodies was positive in seven (24.1%) patients. The age range of the patients was 20–63 years (mean (SEM) 40 (5) and the median (SEM) disease duration was 5.5 (5) years. Patients were receiving no medication or had received any immunosuppressive for at least three months. Controls were 12 aged and sex matched healthy volunteers with an age range from 27–51 years.

Table 1 summarises lymphocyte phenotypes in patients with SSc and healthy controls.

We found a higher expression of T cell activation marker CD25+ and NK cell main surface marker CD56+. In lymphocyte pheno- types there was not any difference among disease subsets and CD25+ and CD56+ were not correlated with the disease duration.

Immunologic abnormalities have been suspected in the development of SSc because of the presence of autoantibodies, changes in cytokine production and evidence of overlap with other autoimmune diseases. It was suggested that immune system changes play the major part in the development of vasculopathy and fibrosis. Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendro et al3 demonstrated that there was no significant difference in the levels of CD4+ and CD8+ in 22 SSc patients and control group but in rheumatoid arthritis (RA) CD3+ and CD8+ in SSc patients and control group but in rheumatoid arthritis (RA) CD3+ and CD8+, in Sjögren’s syndrome CD3+, CD4+ and CD8+ levels were significantly decreased compared with those of controls and they suggested that the abnormalities in immune regulatory T cell circuits leading to autoimmunity are different in each connective tissue disease.

Table 1 Lymphocyte phenotypes in patients with SSc and healthy controls

<table>
<thead>
<tr>
<th>Serum</th>
<th>Systemic sclerosis (n=29)</th>
<th>Control (n=12)</th>
<th>t test</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>C3 (%)</td>
<td>71 (9)</td>
<td>69 (9)</td>
<td>0.660 &gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C4 (%)</td>
<td>44 (9)</td>
<td>45 (9)</td>
<td>0.110 &gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C1INH (%)</td>
<td>31 (9)</td>
<td>26 (9)</td>
<td>1.914 &gt;0.05</td>
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<tr>
<td>C4/CD4</td>
<td>1.56 (0.6)</td>
<td>1.84 (0.6)</td>
<td>1.339 &gt;0.05</td>
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<tr>
<td>D (%)*</td>
<td>12 (3)</td>
<td>13 (3)</td>
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<td>CD25 (%)</td>
<td>18 (9)</td>
<td>7 (1)</td>
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<td>CD56 (%)</td>
<td>22 (9)</td>
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*Unpaired Student’s t test. Data shown as mean (SD).

7 Giacomello A, Taccari E, Zoppini A. Marked decline of visual acuity and azathioprine 2.5 mg/kg/day was prescribed. Two weeks later she was admitted to the hospital because of microscopic haematuria. She was ANA negative, the anti-DNA and serum complement levels were within normal range. Her glomerular filtration rate was 67 ml/min. An open renal biopsy showed diffuse proliferative glomerulonephritis and weak focal segmental positivity of IgA and IgM. She was treated with three boluses of 1 g methylprednisolone and was discharged prescribed azathioprine 150 mg/day, aspirin 300 mg/day and prednisone 30 mg/day. She was well except for occasional mucocutaneous symptoms and a mild local episode during the next four years. However her renal function deteriorated progressively despite uninterrupted treatment with azathioprine and changing doses of prednisone and she was put on regular haemodialysis two years later. Her glomerular filtration rate was 7 ml/min. A graft biopsy performed at that time showed diffuse proliferative glomerulonephritis.

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CD25+ is one of the subunits of high affinity interleukin-2 receptor, which plays a significant role in the pathogenesis of SSc. The percentage of CD25+ T lymphocytes might play only a minor part in the pathogenesis of SSc. CD25+ is one of the subunits of high affinity interleukin-2 receptor and we could not observe any difference in the levels of CD25+ T cells. We can say that B lymphocytes might play only a minor part in the pathogenesis of SSc. CD25+ is a cell surface marker of B lymphocytes and we could not observe any difference in the levels of CD19+ thus we reported that CD8+ suppressor/cytotoxic T lymphocytes and we could not observe any difference in the levels of CD8+ T lymphocytes.

Presence of autoantibodies and hypergammaglobulinemia support the role of humoral immunity but B lymphocytes were rarely found in the skin biopsy specimens. CD19+ is a cell surface marker of B lymphocytes and we could not observe any difference in the levels of CD19+ T cell subpopulations and lymphocytes and we could not observe any difference in the levels of CD8+ T lymphocytes.

The considerable increase in pericardial fluid effusion and classic acute pericarditis to cardiac tamponade and classic acute pericarditis to cardiac tamponade. The two dimensional echocardiogram showed white blood cell count of 56,000/mm³ of an orange fluid was aspirated. Examination of the pericardial fluid showed a white blood cell count of 31,000/mm³ with 96% polymorphonuclear cells. The pericardial fluid was negative for malignant cells.

The patient was treated with high dose corticosteroids and azathioprine. Pericardial fluid samples were obtained by percutaneous aspiration. The pericardial fluid samples were sent for cytological and non-inflammatory heart disease analysis. Mononuclear cells were seen in the pericardial fluid. The percentage of CD4+ T cells and CD8+ T lymphocytes is still obscure. In the presence of azurophil granules in their cytoplasm and they commonly express certain cell surface markers such as CD16+ and CD56+, which is a homofucoid molecule that belongs to the immunoglobulin superfamily. NK cells are the main cellular effector cell and they are highly dependent on cell cytotoxicity. They mediate antigen presentation and secrete immune modulator cytokines such as interferon, IL-2, colony stimulating factor, and other cytokines. The cytokine concentrations were higher in PF than PB. IL-6 has been found to be higher in the pericardium than in serum. Our case, IL6 is usually expressed or increased in the affected organ or system rather than PB. IL-6 has been found to be higher in cerebrospinal fluid and urine than in serum of SLE patients with CNS disease and active nephritis respectively.

The decreased pericardial lymphocyte count and fluid characteristics observed here are in agreement with other studies. The higher frequency of CD4+ T cells and NK cells in PF could be associated with the observed cytokine concentration pattern. For example, CD4+ memory T cells from SLE patients highly secrete IL10 compared with normal controls.

In summary, different patterns of lymphocyte populations and cytokines were found in both sources, with type 2 cytokines predominating in PF and type 1 in PB. Further studies would be required to confirm the results presented here. In addition, immunocytochemical studies of pericardial...
tissue are necessary as the composition of lymphocyte and cytokine profiles may differ between pericardial fluid and tissue.

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Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Lymphocytes (no/mm³)</td>
<td>2425.60 (964.44)</td>
<td>2567.74 (820.72)</td>
</tr>
<tr>
<td>CD3 (no/mm³)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (586.68)</td>
</tr>
<tr>
<td>(%)</td>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
</tr>
<tr>
<td>CD4 (no/mm³)</td>
<td>1032.91 (489.16)</td>
<td>1027.92 (475.56)</td>
</tr>
<tr>
<td>(%)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
</tr>
<tr>
<td>CD8 (no/mm³)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
</tr>
<tr>
<td>(%)</td>
<td>29.25 (8.81)</td>
<td>26.72 (6.81)</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.70 (0.89)</td>
<td>1.39 (0.78)</td>
</tr>
<tr>
<td>CD19 (no/mm³)</td>
<td>266.87 (227.44)</td>
<td>335.90 (142.35)</td>
</tr>
<tr>
<td>(%)</td>
<td>10.81 (6.55)</td>
<td>13.64 (5.09)</td>
</tr>
<tr>
<td>CD4CD45R+ (no/mm³)</td>
<td>406.17 (304.18)</td>
<td>657.70 (301.36)</td>
</tr>
<tr>
<td>(%)</td>
<td>16.70 (9.99)</td>
<td>25.20 (7.76)</td>
</tr>
<tr>
<td>CD4CD45R− (no/mm³)</td>
<td>661.53 (338.48)</td>
<td>529.41 (219.04)</td>
</tr>
<tr>
<td>(%)</td>
<td>27.00 (7.84)</td>
<td>20.77 (6.40)</td>
</tr>
<tr>
<td>NK (no/mm³)</td>
<td>300.45 (179.63)</td>
<td>323.80 (182.53)</td>
</tr>
<tr>
<td>(%)</td>
<td>13.30 (7.76)</td>
<td>12.81 (5.86)</td>
</tr>
</tbody>
</table>

AU = anterior uveitis, NK = natural killer cells, NS = not significant. Data shown as mean (SEM).

Figure 1 Absolute values of CD4CD45R+ cells. Patients with IAU had absolute values lower than the control group, and percentages lower than those of SA patients (p<0.001).

Figure 2 Percentages of CD4CD45R− cells. Patients with IAU had higher percentages than the healthy subjects and SA patients (p<0.001).

Abbreviations as in figure 1.
MATTERS ARISING

RS3PE: six years later

We read with interest the paper by Cantini et al and would like to comment on it.1

In 1992 we performed a retrospective multicentre study on 27 RS3PE patients. We concluded that personal pathogenetic link between both diseases. The immunological features studied with syngeneic and cellular, in HLA-B27+ patients without associated SA were similar to those of patients with SA, which suggest a common pathogenetic link between both forms of AU. It is possible that the long term follow up of these patients will clarify whether or not it is the same entity.

We are indebted to Ms E Velasco for assistance in the preparation of the manuscript.

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4 Brewerton DA, Cañellas, Josep Pujol, Anna Lafont. Pons, Isabel Rotés, Raimon Sanmartí, Eduardo Germans Trias i Pujol, C/ de Canyet s/n, Badalona 08016, Spain
6 Scharf J, Scharf J, Haim T, Nahir M, Gideoni O, et al. A defect of immunoregulatory T cell subsets in systemic rheumatic diseases (one patient) and evolution to haemolytic anaemia and polylymphagymic syndromes (one patient) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymptomatic and 12 required treatment. This was reported elsewhere.1

Now, six years later, we have reviewed the original cohort of patients with the RS3PE syndrome. A questionnaire was sent to the participating rheumatologists. The survey focused on articular symptoms, treatment and evolution. The current cohort was composed of 22 patients (male 16; female 6; mean age:77.9; range 64–91). Four patients died (the three with haemolytic anaemia, one stroke) and one was not located. Thirteen patients were asymptomatic and without treatment, in contrast four required treatment, namely corticosteroids (6), gold salts (1), colchicine (1) and NSAID (1). Interestingly, two of the patients were identified by their rheumatologist as having a seronegative rheumatoid arthritis, another patient had a chronic disease with separate corticosteroid responsive episodes of bilateral hand oedema and polylymphagymic syndromes at different times. Last but not least one patient developed Raynaud’s phenomena, both hands had sclerodactyly. A nailfold capillary microscopy showed a decreased number of capillary loops, which were widened, suggesting systemic sclerosis.

Our results suggest that RS3PE syndrome has a good prognosis. However half of the RS3PE patients are asymptomatic and without treatment six years later. However, there is a subset of patients that have other diseases. Although pure RS3PE syndrome does exist the evolution should be carefully monitored.

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XAVIER TENA
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Authors’ reply

We appreciate the comment by Olivé et al on our article on RS3PE. They reviewed 27 previously described RS3PE patients after a follow up of six years.

As we suggested in a previous report, they confirm that RS3PE syndrome should be considered a heterogeneous condition associated with different inflammatory rheumatic diseases and also with neoplastic disorders.

In our study none of the 23 patients with RS3PE syndrome developed clinical manifestations supporting the diagnosis for another disease. The different study design and selection of patients may in part explain the subset of patients with other diseases and with a worse prognosis observed by Olivé et al.

We designed a prospective follow up study including patients satisfying the criteria for the diagnosis of polymyalgia rheumatica, rheumatoid arthritis and seronegative spondyloarthropathies. Moreover, patients with a clinical history of cancer were excluded from the study. In their original report these authors performed a retrospective study including all patients with distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondyloarthropathies, which may be associated with distal extremity swelling with pitting oedema.2

However, in their retrospective evaluation Olivé et al found that 13 of 22 (59%) patients were asymptomatic and drug free over a six year follow up period, confirming that RS3PE not associated with other conditions and with a good prognosis does exist.

The problem is how to label this clinical picture. As discussed in our article, the similarities of demographic, clinical and MRI findings between patients with “pure” RS3PE syndrome and those with polymyalgia rheumatica and the concurrence of the two syndromes suggest that these conditions may be part of the clinical spectrum of the same disease. In the series of Olivé et al the patient with a clinical course characterised by alternating relapses having RS3PE, pitting oedema or polymyalgic symptoms further supports our hypothesis. Even those RS3PE patients successively diagnosed as having seronegative rheumatoid arthritis (elderly onset) or polymyalgia rheumatica do not conflict with our conclusions. Healey described patients who developed episodes of polymyalgia rheumatica and seronegative rheumatoid arthritis at different times during follow up. Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis followed up over a 42 year period. Four of the six patients who fulfilled the criteria for the diagnosis of rheumatoid arthritis during the follow up experience multiple simultaneous episodes of symmetrical arthritis, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.3

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Crysalis in arthritis: new age nonsense or novel therapeutic target?

Apatite crystals are present in up to 70% of fluids from degenerated joints. Their presence correlates strongly with radiographic evidence of cartilage degeneration and is associated with larger joint effusions when compared with joints without crystals.1 Whether the presence of apatite crystals is a cause of cartilage damage or an effect of cartilage damage is unclear.2 Several lines of evidence suggest that apatite crystals cause joint destruction. For example, apatite crystals induce both mitogen-activated protein kinases (MAPK) and protein kinase C (PKC).3 Furthermore, such activation is specific as the crystals do not activate protein tyrosine kinases (PTK) and activator protein 1 (AP-1).4 They also induce mitogen activated protein kinases (MAPK) and protein kinase C (PKC).5,6 Importantly, such activation thus allows us to target important pathogenic mediators. While it might be tempting to write apatite crystals off as new age nonsense, a considerable body of evidence suggests that, like cytokines, they could serve as a novel therapeutic target as well as a prognostic marker. Without further study, only those with crystal balls can tell.

Geraldine M McCarthy
Department of Clinical Pharmacology, Royal College of Surgeons in Ireland and Mater Misericordiae Hospital, Dublin

Author's reply

We agree with all the points made by Dr McCarthy. Basic calcium phosphates (BCPs) in synovial fluids may be important, and it may be that their identification will be validated in relation to future treatments. However, she seems to agree with the only two points made about BCPs in our article (which is about the identification of urate and pyrophosphate crystals): that is, that on the basis of current understanding BCPs are of doubtful significance, and that their identification should have no influence on contemporary therapeutic decisions.

Paul Dieppe
MRC Health Services Research Collaboration, University of Bristol

Mortality in rheumatoid arthritis patients

The paper “Mortality in rheumatoid arthritis patients with disease onset in the 1980s” is of considerable interest.1 A decrease in mortality risk for rheumatoid arthritis (RA) patients in more recent years would be important, and it is only in the first 10 years of RA. However, this inception cohort differs from those previously published so that no direct comparison is possible. As earlier (and older and larger) studies have shown standardised mortality ratios of two to three, a finding of “normal” mortality might imply that more recently used treatment strategies are reversing the excessive mortality in RA previously reported.2

Yet, even at first perusal, there are a lot of deaths in this series of relatively young people. In the 10 years after a mean age of 51, 18 patients (10%) had died. Over 20 deaths were said to be “expected”. However, using US mortality rates for a population mean aged the same, projected over 10 years, two thirds women, and white, one would expect only 11 deaths using 1996 mortality rates and 12 deaths using 1985 rates, over the 1710 patients years of follow up. While we did not have the age distribution of this RA cohort to calculate precise expectations, these figures should be conservative. Female mortality rates in the US white female popula-
tion, at 3.4 per 1000 per year at age 51 and 9.0 per 1000 per year at age 61 are presumably higher than those in long lived Malmöhus County, Sweden.

Of interest, in our own larger study with meticulously computed “expected” values in four different populations we also had an “expected” death rate of about 10% to 15% over 10 years. But, these were not inception cohorts and their age at start of follow up was 60.4, 62.6, 59.8, and 69.1 years. Thus, they were much older cohorts. Given the expected doubling of mortality rates each eight years (Gompertz’s law), expected deaths should have been two to three times more in our cohorts than in a cohort beginning at age 51.

Finally, recent studies have not suggested that “rheumatoid” deaths in themselves are the cause of the increased mortality in RA. The observed “excess” deaths are spread around in multiple disease categories, with accelerated atherosclerosis numerically the largest problem and only a slight relative increase in systemic RA complications, gastrointestinal haemorrhage, and infections.

Authors’ reply

We were pleased to notice the interest in our paper shown by Drs Fries and Bloch. In reply to their comments we do not consider the death rate of 10% in the cohort as an excessive one compared with the age and sex matched general population. It is not possible to calculate more precise figures of expected deaths knowing the mean age of the cohort only. To clarify this and make comparison possible we enclose a table of the age distribution in our cohort in five year intervals giving the number of observed and expected deaths for each age interval separately.

Women do live longer in Malmöhus County, Sweden than in the US. Female mortality rates in Malmöhus County were 3.76 per 1000 at age 51 and 7.32 per 1000 at age 61 in 1985. In 1996 the corresponding figures were 2.03 per 1000 at age 51 and 3.39 per 1000 at age 61.

We agree that the main cause of death in RA patients very seldom is the rheumatoid disease in itself. This was true also for our study where no certain connection between RA and death was found in any of the cases.

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KERSTIN EBERHARDT
Department of Rheumatology, Lund University Hospital, Sweden

Table 1

<table>
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<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
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<td>20-24</td>
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HLA-B27+ anterior uveitis with or without associated spondyloarthritis: clinical and immunological features
FRANCISCO RIVERA-CÍVICO, JUAN JIMÉNEZ-ALONSO, MARÍA MARTIN-ARMADA, MARÍA TERESA HERRANZ, JOSÉ CASTRO, FRANCISCO PEREZ-ALVAREZ, J L DEL ARBOL, MANUEL TORIBIO and FRANCISCO SAMANIEGO

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