Letters

A successful renal transplantation in Behçet’s syndrome

Renal involvement is not frequent in Behçet’s syndrome (BS) and consists of occasional reports of patients suffering from glomerulonephritis, 
IgA nephropathy and renal amyloidosis. 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. In brief, she was 21 years old when she developed recurrent oral and genital ulcers, bilateral ureters, 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 pathology reaction was positive and she was diagnosed as B1A2 B4. 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 administered. 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 the 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 haemodialysis 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 in the 14th month of haemodialysis. She received a kidney from her mother. The graft function started immediately and she was prescribed maintenance immunosuppression with azathioprine, cyclosporin A and methylprednisolone. An acute intussusception type rejection on the 11th day of transplantation was treated successfully with pulsed corticosteroids. Now 40 months after transplantation, she has normal renal function and is free of any symptoms of BS except for occasional oral ulcers.

We had some hesitation in performing a renal transplantation in our patient initially because of the lack of any previous experience and particularly because of our concern for the heightened inflammatory response of BS patients to simple penetrating trauma that is best characterised by the pathergy reaction. This reaction, however, is not only limited to the skin and development of aneurysms after vascular punctures and episodes of synovitis after arthrocentesis have been observed. Furthermore, postoperative complications leading to a poor outcome such as occlusions of grafts/anastomoses after the surgical treatment of aneurysms or perivalvular leakage and suture breakdown after aortic valve replacement have been reported in BS patients. As these complications are probably related to the pathergy phenomenon reaction, you would also reasonably expect problems after an organ transplantation, an operation with arterial and venous anastomoses. On the other hand, we had previously shown that despite the increased inflammation, wound healing after full thickness skin punch biopsies is not changed in BS. We have not experienced any of the feared complications after the transplantation procedure in this instance. One reason for this favourable outcome might be that our patient was female. It is known that BS runs a milder disease course in women compared with men. Additionally, the rather intensive immunosuppressive/anti-inflammatory post-transplant drug use might also have contributed to the diminished disease activity of our patient as well as to the prevention of a reaction at the site of transplantation. Whatever it might be related to, the outcome in our patient suggests that BS patients can undergo renal transplantation with a satisfactory outcome.

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13 Yazici H, Tuzun Y, Pazarli H, Yurdakul S, Ozyazgan Y. Oropharyngeal disease course in women compared with men.]*

Lymphocyte phenotypes in systemic sclerosis

Although the pathophysiology of systemic sclerosis (SSc) is not fully clarified, there are considerable data implicating abnormalities of microvascular changes, fibroblast activation and immune system abnormalities. Immunologic system activation is a pathogen as a stimulus in both fibrotic and vascular damage. To investigate the immune system abnormalities in the pathogenesis of SSc we evaluated lymphocyte phenotypes in patients with SSc and healthy controls. Analysis of surface markers (Epics Profile II) for total T (CD3), T helper (CD4), T suppressor (CD8), B lymphocyte cell surface marker (CD19), activation marker (CD25) and natural (NK) cell surface marker NKH-1 (CD56).

We studied 29 patients (27 women, two men) 16 limited, 12 diffuse and one overlap who fulfilled preliminary criteria for classification of SSc. 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 mean (SEM) disease duration was 5.6 (5.5) years. Patients were receiving no medication nor had received any immunosuppressive agent for at least three months. Controls were 12 age and sex matched healthy volunteers with an age range from 27–51 years.

Data were compared for significance for Student’s unpaired t test.

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 no any difference among disease subsets and CD25+ and CD56+ were not correlated with the disease duration.
- Immune system abnormalities have been suspected in the development of SSc because of the presence of autoantibodies, changed cytokine production and evidence of overlap with other autoimmune diseases. It was suggested that immune system changes play the major part for the development of vascular and fibrosis. Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendro et al demonstrated that there was no significant difference in the levels of CD3+ and CD8+ in 22 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 subjects (n=12)</th>
<th>t Test*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3D%</td>
<td>(71 (9)</td>
<td>69 (9)</td>
<td>0.660&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C4D%</td>
<td>(44 (9)</td>
<td>45 (9)</td>
<td>0.110&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C5D%</td>
<td>(31 (9)</td>
<td>26 (9)</td>
<td>1.914&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C4/CD8</td>
<td>1.56 (0.6)</td>
<td>1.84 (0.6)</td>
<td>1.339&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>C19%</td>
<td>(12 (3)</td>
<td>13 (5)</td>
<td>0.445&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>CD25%</td>
<td>(18 (9)</td>
<td>7.1 (3)</td>
<td>4.150&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>CD56%</td>
<td>(22 (9)</td>
<td>14 (5)</td>
<td>2.691&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

*Unpaired Student’s t test. Data shown as mean (SD).
Lymphocyte populations and cytokine concentrations in pericardial fluid from a systemic lupus erythematosus patient with cardiac tamponade

Pericardial involvement is the most common cardiovascular complication in systemic lupus erythematosus (SLE). The clinical picture varies from subclinical pericardial effusion and classic acute pericarditis to cardiac tamponade. In a recent review of pericardial fluid (PF) cytokines, the frequency of lymphocyte populations and cytokine concentration pattern in PF and peripheral blood (PB) from a SLE patient with cardiac tamponade were determined. 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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HLA-B27+ anterior uveitis with or without associated spondyloarthritides: clinical and immunological features

Anterior uveitis (AU) is the most common form of uveitis, and may be produced by different causes. An aetiologic diagnosis is commonly established in approximately half of the patients with AU by being seronegative spondyloarthropathies (SA), and mainly ankylosing spondylitis, the most frequent cause of the disease. Approximately 50% of the patients with AU are HLA-B27 positive; half of them usually present with associated SA. The other half are patients with HLA-B27+ but with no associated articular disease (HLA-B27+ AU). Several clinical features have been described to be common in patients with AU associated with HLA-B27, however, these features are similar either in patients with or without associated SA. This is why we conducted this clinical and immunological study in patients with AU positive for HLA-B27 with the aim of discovering the differences between patients with and without associated SA.

A prospective study was conducted involving 146 patients with AU seen between April 1988 and October 1995 referred to an ophthalmologist with the syndromic diagnosis of AU of unknown origin. Patients were classified in three aetiological groups: (1) Idiopathic anterior uveitis (IAU), all were HLA-B27−; (2) HLA-B27+ AU without associated SA, and (3) HLA-B27+ AU with associated SA.

Of the 146 patients with AU studied, 98 had IAU (67.1%) and 48 were positive for HLA-B27 of them, 19 (13%) had associated SA (HLA-B27+ AU with SA), and 29 (19.9%) did not (HLA-B27+ AU). No significant differences were found in clinical features of AU between the three study groups. Erythrocyte sedimentation rate, C reactive protein and IgA were found to be more increased in patients than in control, although without differences between the three groups of patients. With regard to lymphocyte populations, we found some differences between our AU patients and control group (table 1). Patients with IAU showed lower percentages (mean (SEM)) of CD4CD45R+ (15.47 (9.49)%) than controls (25.20 (7.76)%) and patients with SA (21.97 (10.16)%) (fig 4). Patients with IAU had higher percentages of CD4CD45R− (24.67 (7.89)%) than SA patients (23.23 (6.81)%) and the control group (20.77 (6.40)%) (fig 5).

Associated systemic pathology was demonstrated in 13% of the cases (19 patients with seronegative SA), 29 patients (19.9%) were HLA-B27+ without SA; not associated disease was found in the other 98 cases of AU (67.1%), which were classified as idiopathic. Seronegative SA are the most frequent entities found in uveitis patients, representing between 6% and 13% of all forms of uveitis, and 20 to 25% of the AU. HLA-B27+ AU without associated SA represents about 25% of the AUs; it has been considered by some authors a ‘frustrated’ or monosymptomatic form of ankylosing spondylitis, but today, it is still unclear as to whether or not it is the same clinical entity, or whether these patients will develop seronegative SA in future. It did not find differences in clinical features of AU between HLA-B27+ and HLA-B27− patients. A deficit of CD4CD45R+ (suppressor-inducer T lymphocytes) and an increase of CD4CD45R− (memory T lymphocytes), such as in our patients with IAU, have been described in certain autoimmune disease, suggesting that these disorders could be attributable to these changes. In addition, differences found in the values of CD4CD45R cells between patients with IAU and SA suggest a different physiopathogenetic mechanism in the development of both.

Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th></th>
<th>AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (no/mm³)</td>
<td>2425.60 (964.44)</td>
<td>2567.74 (820.72)</td>
<td>NS</td>
</tr>
<tr>
<td>CD3 (no/mm³)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (586.68)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (no/mm³)</td>
<td>1023.91 (489.16)</td>
<td>743.83 (47.56)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(%)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD8 (no/mm³)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>29.25 (8.81)</td>
<td>26.72 (6.81)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.70 (0.89)</td>
<td>1.32 (0.78)</td>
<td>NS</td>
</tr>
<tr>
<td>CD19 (no/mm³)</td>
<td>266.87 (227.44)</td>
<td>335.90 (142.35)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>10.81 (5.65)</td>
<td>13.64 (5.09)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD45R+ (no/mm³)</td>
<td>406.17 (304.18)</td>
<td>657.70 (301.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(%)</td>
<td>16.70 (9.99)</td>
<td>25.20 (7.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD45R− (no/mm³)</td>
<td>661.53 (338.48)</td>
<td>529.41 (219.04)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(%)</td>
<td>27.00 (7.84)</td>
<td>20.77 (6.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NK (no/mm³)</td>
<td>300.45 (179.63)</td>
<td>323.80 (182.53)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>13.30 (7.76)</td>
<td>12.81 (5.86)</td>
<td>NS</td>
</tr>
</tbody>
</table>

IAU = 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 less than the control group, and percentages lower than those of SA patients (p<0.001). IAU= idiopathic anterior uveitis; AU= anterior uveitis; SA= spondyloarthritides.

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 of 27 RS3PE patients. We concluded that personal history of polymyalgia rheumatica (two patients), presence of erosions (one patient) and evolution to haematological disorders (two patients concomitantly developed a T lymphoblastic lymphoma, one a myeloproliferative syndrome) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymptomatic and 15 required treatment. This was reported elsewhere.2

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, treatments 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 haematological disorders, one stroke) and one was not located. Thirteen patients were asymptomatic and without treatment, in contrast nine required treatment, namely corticosteroids (6), gold salts (1), clofazimine (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 polyarthralgic 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 in the first half of the 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.

**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 atherosclerotic 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 excluding patients satisfying the criteria for the diagnosis of polymyalgia rheumatica, rheumatoid arthritis and seronegative spondylarthropathies. 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 remitting distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondylarthropathies, which may be associated with distal extremity swelling with pitting oedema.

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,3 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 altitudinal relapses has RS3PE and pitting oedema or polyarticular symptoms further supports our hypothesis. Even those RS3PE patients successively diagnosed as having seronegative rheumatoid arthritis (elderly onset rheumatoid arthritis) 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.4 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 experienced multiple separate episodes of symmetrical arthritis, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.5

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

Apatite crystals are present in up to 70% of fluid 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. Whether the presence of apatite crystals is a cause of cartilage damage or an effect of cartilage damage is unclear. Several lines of evidence suggest that apatite crystals cause joint destruction. For example, apatite crystals induce both mitogenic and proinflammatory synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloproteinases (MMPs) synthesis and secretion, thus promoting tissue damage.

The cellular mechanisms whereby apatite crystals induce such responses are currently under investigation. Like many other growth promoting agents, apatite crystals activate phosphatidylinositol 3-kineses (PI3K).

Currently, there is no drug available to retard the progression of OA. A greater understanding of the pathogenesis of OA is essential to the development of rational treatments that allow 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 they could serve as a novel therapeutic target as well as a prognostic marker. Without further study, only those with crystal balls can tell.

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 our current understanding alone, the identification does not have the age distribution of this RA group. We do not have the age distribution of this RA group. We are therefore somewhat cautious about the significance of such studies and that their identification will be valuable in relation to future treatments. We agree with all the points made by Dr McCarthy.

Mortality in rheumatoid arthritis patients

The paper “Mortality in rheumatoid arthritis patients with disease onset in the 1980s” is of considerable interest. A decrease in mortality risk for rheumatoid arthritis (RA) patients in more recent years would be important, particularly 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.
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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DANIEL A BLOCH

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Authors’ reply


Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
<th>Observed mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20–24</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25–29</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30–34</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35–39</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
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Lymphocyte phenotypes in systemic sclerosis

EDIZ DALKILIÇ, KAMIL DILEK, MUSTAFA GÜLLÜLÜ, MAHMUT YAVUZ, YÜKSEL KARAKOÇ, MUSTAFA YURTKURAN, FERAH BUDAĞ and GÜHER GÖRAL

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