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 with glomerulonephritis, IgA nephropathy and renal amyloidosis.1 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 the patient carried the 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 introduced. 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 haematuric 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 twice a week. 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 interstitial 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.1 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.4 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 replacement1 have been reported in BS patients. As these complications are probably related to the pathergy phenomenon of BS, 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.9 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.10 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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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 recent years, several studies of pericardial fluid (PF) have been limited to immunological analysis. Mononuclear cell populations and cytokines were found in both PF and peripheral blood (PB), with type 2 cytokines predominating in PF and type 1 in PB. The decrease in pericardial lymphocyte count and fluid characteristics observed here is in agreement with other studies. The higher frequency of CD4+ T cells and NK cells in PB could be associated with the observed cytokine concentration patterns. 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 fluid concentrations of IL6, not only can increase anti-inflammatory activity and the frequency of lymphocytes was determined by flow cytometry. The cytokine concentrations from plasma and PF were determined by ELISA. Table 1 shows the results. Among lymphocytes, the percentage of CD4+ T cells and NK cells was higher in PF, while the frequency of CD8+ T cells was higher in PB. IL6 concentration was much higher in PF than in PB. Also, IL1B and IL10 concentrations were higher in PF. IL2 was detected in plasma but not in PF.

The considerable increase in pericardial IL6, with respect to peripheral blood, was of interest. PF concentrations of IL6 in our case were substantially higher than those observed in PF from patients with inflammatory and non-inflammatory heart conditions. IL6, not only can increase anti-body production, but in SLE, B cells have increased reactivity to this cytokine. As in our case, IL6 is usually expressed or increased in the affected organ or system rather than PB. IL6 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 is in agreement with other studies. The higher frequency of CD4+ T cells and NK cells in PB could be associated with the observed cytokine concentration patterns. For example, CD4+ memory T cells from SLE patients highly secrete IL10 compared with normal controls.

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tissue are necessary as the composition of lymphocyte and cytokine profiles may differ between pericardial fluid and tissue.

Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>AU patients (n=146)</th>
<th>Controls (n=311)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (×10⁶/mm³)</td>
<td>CD3 (×10⁶/mm³)</td>
<td>CD4 (×10⁶/mm³)</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>2425.60 (964.44)</td>
<td>1734.20 (726.67)</td>
<td>1023.91 (489.16)</td>
</tr>
<tr>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
<td>42.56 (9.50)</td>
</tr>
<tr>
<td>1219.70 (427.56)</td>
<td>1835.64 (586.68)</td>
<td>47.90 (17.56)</td>
</tr>
</tbody>
</table>

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= spondyloarthritis.

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).

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.

HLA-B27+ anterior uveitis with or without associated spondyloarthritis: clinical and immunological features

Anterior uveitis (AU) is the most common form of uveitis, and may be produced by different causes. An aetiological diagnosis is necessary as the composition of lymphocyte and cytokine profiles may differ between pericardial fluid and tissue. 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 from 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 (67.1%) were classified in the clinical entity of anterior uveitis (IAU), 29 patients (19.9%) were HLA-B27+ AU with associated SA, and 20 to 25% of the AU. HLA-B27+ AU without associated SA represents about 25% of the AU; it has been considered by some authors a “frustrated” or nonsymptomatic form of ankylosing spondylitis, but today, it still unclear as to whether or not it is the same clinical entity, or whether these patients will develop seronegative SA in future. We 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 diseases, 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 diseases.

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diseases. The immunological features studied were with synovial and cellular, in HLA-B27+. Patients without associated SA were similar to those with patients of 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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MATTERS ARISING

RS3PE: six years later

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

In 1992 we performed a retrospective multicentre study of 27 RS patients. We concluded that personal history of polymyalgia rheumatica (two patients), presence of erosions (one patient) and evolution to haematological diseases (two patients concomitantly developed a T lymphoma and one myelodysplastic syndrome) 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.

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 (16 male; 6 female; mean age:77.9; range 64-91). Four patients died (the three with haematological diseases, 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), clo- roquine (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 polyynalgic 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 and 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 closely monitored.

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We thank the following rheumatologists for the contribution to the study: Jordi del Blanco, Miqual Pons, Isabel Rotés, Raimon Santamaría, Eduardo Kantarewicz, Miquel Sala, Ivonne Brysse, Rosa Roselló, Javier Arasa, Marta Larrosa, Genonima Cifuentes, Josep Pujol, Anna Lafont.

Authors’ reply

We appreciate the comment by Olíve 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 features 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 Olíve 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 Olíve 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 Olíve et al the patient with a clinical course characterised by alternative relapses of RS3PE syndrome, pitting oedema or polyynalgic 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.

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.

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

Apatite crystals are present in up to 70% of
fluids from degenerated joints.1 Their presence corre-
lates strongly with radiographic evidence of cartilage
degeneration and is associated with larger joint effusions when compared with
joints without crystals.2 Whether the presence of
apatite crystals is a cause of cartilage damage or an effect of cartilage damage is
unclear.3 Several lines of evidence suggest that
apatite crystals cause joint destruction. For
example, apatite crystals induce both mitogen-
usions and proinflammatory synthesis in synovial
fibroblasts and chondrocytes in vitro.3 They
also induce matrix metalloproteinase (MMP)
synthesis and secretion, thus promoting tissue
destruction.4 The cellular mechanisms whereby
apatite crystals induce such responses are cur-
rently under investigation. Like many other
growth promoting agents, apatite crystals
induce a variety of transcription factors such as
nuclear factor-kappa B (NF-kB) and activator
protein 1 (AP-1).5 They also induce mitogen
activated protein kinases (MAPK) and protein kinases C (PKC).6
Furthermore, such activa-
tion is specific as the crystals do not activate
protein tyrosine kinases (PTK) or phosphati-
dylinositol 3-kinases (PI3K).7 If the
crystals were present simply as a consequence of joint
destruction, we would expect them to be
present in other arthropathies characterised by
cartilage dissolution and synovial lining prolif-
eration such as rheumatoid arthritis (RA). How-
ever, apatite crystals are rarely found in
RA joint fluids.8 Thus, current data suggest that
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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 signifi-
cance", and that their identi-
fication should have no influence on contem-
porary therapeutic decisions.

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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 mortal-
ity risk for rheumatoid arthritis (RA) patients in
more recent years would be important, especially
only in the first 10 years of RA. How-
ever, this inception cohort differs from those
previously published so that no direct com-
parison is possible. As earlier (and older and
larger) studies have shown standardised mor-
tality ratios of two to three, a finding of "nor-
mal" mortality might imply that more
recently used treatment strategies are rever-
sing the excessive mortality in RA previously
reported.

Yet, even at first perusal, there are a lot of
deads 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 "natural". 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 mor-
tality rates in the US white female popula-

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phate crystal-induced activation of human
fibroblasts. Role of nuclear factor-kb, activator
protein 1 and protein kinase C. J Biol Chem
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.

JAMES F FRIES
Daniel A Bloch
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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.

ELISABET LINDQVIST
KERSTIN EBERHARDT
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<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
<th>Observed mortality</th>
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<td>15-19</td>
<td>1</td>
<td>0</td>
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<tr>
<td>20-24</td>
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<td>7</td>
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<tr>
<td>30-34</td>
<td>3</td>
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<tr>
<td>35-39</td>
<td>15</td>
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<td>40-44</td>
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<td>45-49</td>
<td>27</td>
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<td>55-59</td>
<td>24</td>
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<td>70-74</td>
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<tr>
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<td>All</td>
<td>183</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, JOSE CASTRO, FRANCISCO PEREZ-ALVAREZ, J L DEL ARBOL, MANUEL TORIBIO and FRANCISCO SAMANIEGO

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