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 uveitis, erythema nodosum, folliculitis, and intermittent arthralgia 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 had a CARD LA BS. It was decided to prescribe only local drops for her mild eye involvement. Three months later she experienced two oculocutaneous episodes resulting in a sharp decline of visual acuity and azathioprine 2.5 mg/kg/day was withdrawn. 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 normal. 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 methylprednisone 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 bilateral follicular episcleritis 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 due to a normal glomerular filtration rate of 67 ml/min. In the 14th month of haemodialysis, she received a kidney from her mother. The graft function started immediately and she was prescribed maintenance immunosuppressive therapy with azathioprine, cyclosporin A and methylprednisolone. An acute interstitial 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 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. 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 the organ transplant.

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. Immune system activation is considered 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 volunteers by flow cytometry (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 5.5 (0.5) 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 not 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 in the development of vasculopathy and fibrosis. Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendrez et al demonstrated that there was no significant difference in the levels of CD4+ and CD8+ among 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</th>
<th>Control</th>
<th>t Test*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (%)</td>
<td>71 (9)</td>
<td>69 (9)</td>
<td>0.660</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>44 (9)</td>
<td>45 (9)</td>
<td>0.110</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>31 (9)</td>
<td>25 (9)</td>
<td>1.914</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.56 (0.6)</td>
<td>1.84 (0.6)</td>
<td>1.339</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>12 (4)</td>
<td>13 (5)</td>
<td>0.445</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD25 (%)</td>
<td>18 (9)</td>
<td>7.1 (3)</td>
<td>4.150</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CD56 (%)</td>
<td>22 (9)</td>
<td>14 (5)</td>
<td>2.691</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*Unpaired Student’s t test. Data shown as mean (SD).
Various results in diminishing the percentage of CD56+ cells in the pathogenesis of SSc, although this finding suggested the role of IL2R and known as the alpha chain of IL2R. CD25+ is one of the subunits of high affinity IL2R and toxic 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 cells. We can say that B lymphocytes might play only a minor part in the pathogenesis of SSc. CD25+ is one of the subunits of high affinity IL2R and known as the alpha chain of IL2R. Bruns et al. established a clear correlation between CD25+ and soluble IL2R in serum. T lymphocytes expressing CD25+ and T helper cell derived cytokines and growth factors stimulate matrix protein synthesis by fibroblasts, resulting in generalised fibrosis and sclerosis. In our study we found significant increases of CD25+ and this surface marker can be used in the follow up the inflammatory stage and activity of SSc. In further studies the investigation of CD25+ T cell subsets CD4+, CD8, TCR gamma-delta and other T cell activation markers HLA-DR, CD45RO/CD45RA will be useful to shed light on the pathogenesis of SSc. NK cell abnormalities have been described in a number of rheumatic diseases such as RA, Sjögren's syndrome, systemic lupus erythematosus. NK cells are large granular lymphocytes easily identified morphologically by the presence of azurophil granules in their cytoplasm and they commonly express certain cell surface markers such as CD16+ and CD56+. CD56+ is a homofluc molecule that belongs to the immunoglobulin superfamily. NK cells are the main cellular effectors of the body dependent cell cytotoxicity, they mediate antigen presentation and secrete immune modulator cytokines like interferon, IL2, colony stimulating factor, these functions suggested the involvement of NK cells in the pathophysiology of SSc. We found the percentage of CD56+ significantly higher in SSc patients (mean SD 22 (9)) than controls (mean SD 14 (5)). Although this finding suggested the role of CD56+ cells in the pathogenesis of SSc, various results in different investigations pointed out that further investigations on CD56+ and CD16+ NK cell percentage and activity are needed.

**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. Immunological studies of pericardial fluid (PF) have been limited to determination of autoantibodies, complements and immune complexes. To further study the pathogenic mechanisms involved in lupus pericardia, we measured the lymphocyte populations and cytokine concentration pattern in PF and peripheral blood (PB) from a SLE patient with cardiac tamponade.

We report a case of a 38 year old man with SLE diagnosed in December 1995 when he presented with polyarthritis, photosensitivity, oral ulcers, nephritis, non-hemolytic anemia, positive ANA, increased anti-dsDNA and hypocomplementaemia. The patient improved with corticosteroids and intravenous cyclophosphamide treatment. However, on 18 June 1997 he presented with syncope, hypotension (80/40 mm Hg), a tachycardia, jugular vein distension and cardiomegaly. The two dimensional echocardiogram showed a large pericardial effusion with right atria and ventricle collapse in diastole. Pericardiocentesis was performed and 180 ml of an orange fluid was aspirated. Examination of PF showed white blood cell count of 5280/mm³ (polymorphonuclear cells = 96%). The absolute number of lymphocytes was lower in PF than in PB (211 × 10⁶/mm³). PF concentrations of IL1B, IL6, with respect to plasma, is particularly interesting. PF concentrations of IL6 in our case, IL6 is usually expressed or increased in the affected organ or system rather than PF, IL6 has been found to be higher in cerebral blood 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>Lymphocytes (no/mm³)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+CD45R+ (no/mm³)</td>
<td>15.4</td>
<td>18.2</td>
</tr>
<tr>
<td>CD4+CD45R+ (%/no/mm³)</td>
<td>378.5</td>
<td>443.1</td>
</tr>
<tr>
<td>CD4+CD45R- (%/no/mm³)</td>
<td>28.5</td>
<td>27.7</td>
</tr>
</tbody>
</table>

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

Figure 1 Absolute values of CD4+CD45R+ cells. Patients with IAU had absolute values lower 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 2 Percentages of CD4+CD45R+ cells. Patients with IAU had higher percentages than the healthy subjects and SA patients (p<0.001). Abbreviations as in figure 1.
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 276 SLE patients. We concluded that personal history of polymyalgia rheumatica (two patients), presence of erosions (one patient) and evolution to haemato logical diseases (two patients concomitantly developed a T lymphoma and one a 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 (male 16; female 6; 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 roquines (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 polyynamylgic symptoms 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. At least 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.

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We thank the following rheumatologists for the contribution to the study: Jordi del Blanco, Miquel Pons, Isabel Rotés, Raumon Sanmartí, Eduard Kantarewicz, Miquel Sala, Ivonne Bryesse, Rosa Roselló, Javier Arasa, Marta Larroza, Genomina Cabellos, Jose Pujol, Anna Lafont.


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 erosions 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 of 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 all features was relapses of RS3PE without oedema or polyynamylgic 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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Correspondence to: Dr F Cantini, 2nd Divisione di Medicina, Ospedale di Prato, Piazza Ospedaledi 1, 59100 Prato, Italy.

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metalloproteinase production in human synovial fibroblasts. Arthritis 
Rheum 1998;41:S300.

**Crystals 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. 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 cytokines in synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloproteinase (MMP) 
synthesis and secretion, thus promoting tissue 
destruction. 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 
uclear factor kappa B (NF-kB) and activator protein 
1 (AP-1). They also induce mitogen activated protein kinases (MAPK) and protein 
kine C (PKC). Furthermore, such activa-
tion is specific as the crystals do not activate protein tyrosine kineses (PTK) or phosphati-
dylinositol 3-kinases (PI3K).

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). However, apatite crystals are rarely found in 
RA joint fluids. Thus, current data support the possibility of apatite crystals being 
a novel therapeutic target. On the other hand, the clinical significance of apatite 
crystals in joint destruction continues to be questioned. Dieppe and Swan doubt that 
apatite crystals are of patho-
genetic significance in arthritis and argue that they fail to refutate the two points made about BCPs in our article: that is, that on the basis of current understandings, there is a “doubtful significance”, and that their identifi-
cation should have no influence on contem-
porary therapeutic decisions.

**Author’s reply**

We agree with all the points made by Dr 
McCarty. Basic calcium phosphates (BCPs) 
in synovial fluids may be important, and it 
may be that their identification will be valuable 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 understandings, there is 
a “doubtful significance”, and that their identifi-
cation should have no influence on contem-
porary therapeutic decisions.

**Paul Dieppe**

MRC Health Services Research Collaboration, 
University of Bristol, Bristol

**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 mortal-
ity risk for rheumatoid arthritis (RA) patients in 
more recent years would be important, 
as we are only in the first 10 years of RA. How-
ever, this inclusion 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 revers-
ing the excessive mortality in RA previously 
observed.

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 
deads were said to be “expected”. However, 
use 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 crystals inhibits a basic calcium phospho-
phosphate dihydrate (CPPD) can be by polarised light microscopy. 
Furthermore, the presence of apatite crystals 
does not change the management of either 
Rheumatoid arthritis (OA) or any other arthropathy 
in patients at present, and we conclude 
therefore that apatite crystals are irrelevant to 
clinical practice. Historically, the role of 
cytokines in the pathogenesis of OA was also 
considered to be speculative. As with apatite 
crystals, levels of pro-inflammatory cytokines like interleukin 
1 (IL1) or tumour necrosis factor a (TNFf) are 
not routinely measured in joint fluid from 
patients with arthritis. After considerable 
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15 McCarthy GM, Kurup IV, Westfall PR. Basic 
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cation should have no influence on contem-
porary therapeutic decisions.

**Paul Dieppe**

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University of Bristol, Bristol
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.

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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.

TABLE 1

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

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