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 having glomerulonephritis,[1] IgA nephropathy[2] 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.[4] 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 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 transient neurological 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 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.[5] 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.[6 7] Furthermore, postoperative complications leading to a poor outcome such as occlusions of grafts/anastomoses after the surgical treatment of aneurysms[8] or perivalvular leakage and suture breakdown after aortic valve replacement[9] 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.[10]

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.[11] 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.

SUHEYLA APAYDIN
EKREM EREK
UGUR ÜLKÜ
Division of Nephrology, Department of Internal Medicine

VEDAT HAMURYUDAN
HASAN YAZICI
Division of Rheumatology, Department of Internal Medicine

MUZAFFER SARIYAR
Department of Surgery, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

Correspondence to: Dr V Hamuryudan, Veysipasa sokak 100, Yil Sitesi, I Blok D16 Uskudar, 81190 Istanbul, Turkey.

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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 may play a part as a stimulus in both fibrotic and vascular damage.[1] To investigate the immune system abnormalities in the pathogenesis of SSc we evaluated lymphocyte phenotypes in patients with SSc and healthy controls by flow cytometry (Epics Profile II) for total T (CD3), T helper (CD4), T supressor (CD8), B lymphocyte cell surface marker (CD19), activation marker (CD25) and natural killer (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.[2] 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 immunsupressive 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 phenotypes 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.[3] Previous reports on T lymphocyte subpopulations in SSc are partially conflicting. Melendro *et al*[4] 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

Serum	*Systemic sclerosis (n=29)*	*Control group (n=12)*	*t Test**	*p Value*
CD3 (%)	71 (9)	69 (9)	0.660	>0.05
CD4 (%)	44 (9)	45 (9)	0.110	>0.05
CD8 (%)	31 (9)	25 (6)	1.914	>0.05
CD4/CD8	1.56 (0.6)	1.84 (0.6)	1.339	>0.05
CD19 (%)	12 (4)	13 (5)	0.445	>0.05
CD25 (%)	18 (9)	7.1 (3)	4.150	<0.05
CD56 (%)	22 (9)	14 (5)	2.691	<0.05

*Unpaired Student's *t* test. Data shown as mean (SD).

Whiteside *et al*[5] and Barrett *et al*[6] by using the indirect immunoflourescence method, reported that CD8+ supressor/cytotoxic T cells are decreased in SSc group, our findings differ from those of Whiteside and Barrett; we and Degiannis *et al*[7] have used the more sensitive flow cytometry method and could not find any difference between T lymphocyte subgroups of SSc patients whereas in the pathogenesis of SSc the role of CD4+ and CD8+ T lymphocytes is still obscure. Presence of autoantibodies and hypergammaglobulinaemia support the role of humoral immunity but B lymphocytes were rarely found in the skin biopsy specimens.[8] CD19+ is a cell surface marker of B lymphocytes and we could not observe any difference in the levels of CD19+ thus 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*[9] 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 homofilic adhesion molecule that belongs to the immunglobulin superfamily. NK cells are the main cellular effectors of antibody 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.[6 10]

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.

EDIZ DALKILIÇ
KAMIL DILEK
MUSTAFA GÜLLÜLÜ
MAHMUT YAVUZ
YÜKSEL KARAKOÇ
MUSTAFA YURTKURAN
Uludag University, School of Medicine, Department of Rheumatology and Nephrology

FERAH BUDAK
GÜHER GÖRAL
Uludag University, School of Medicine, Department of Infectious Disease

Correspondence to: Dr K Dilek, Uludag University Medical Faculty, Department of Nephrology and Rheumatology 16059, Görükle-Bursa, Turkey.

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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).[1] The clinical picture varies from subclinical pericardial effusion and classic acute pericarditis to cardiac tamponade.[1 2] Immunological studies of pericardial fluid (PF) have been limited to determination of autoantibodies, complements and immune complexes.[3 4] To further study the pathogenic mechanisms involved in lupus pericarditis we examined the lymphocytic 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 anaemia, positive ANA, increase of anti-dsDNA and hypocomplementaemia. The patient improved with corticosteroid 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. Pericardiocenthesis was performed and 180 ml of an orange fluid was aspirated. Examination of PF showed white blood cell count of 5280/mm^3 (polymorphonuclear cells = 96%). The absolute number of lymphocytes was lower in PF than in PB (211 *v* 700/mm^3). PF level of protein was 4.1 g/dl (serum = 5.3 g/dl), glucose was 53 mg/dl (serum = 110 mg/dl) and LDH was 471 IU/l (serum = 110 IU/l). PF cultures were negative. No malignant cells were seen. He was treated with high dose corticosteroids and azathioprine. Prednisone was gradually decreased to 10 mg daily over a three month period. After a 22 month follow up, he remained clinically stable without recurrent pericardial involvement or SLE exacerbations.

Table 1 Frequency of lymphocyte populations and cytokine concentrations in peripheral blood and pericardial fluid

Parameter	*Peripheral blood*	*Pericardial fluid*
Lymphocyte population (%)		
Total T cells	57.8	50.0
CD4+ T cells	17.6	25.0
CD8+ T cells	34.3	25.0
B cells	7.8	8.3
NK cells	34.3	41.7
Cytokine concentration* (pg/ml)		
IL1β	<3.0	240.0
IL2	201.8	<4.0
IL4	<6.0	<6.0
IL6	16.9	4714.0
IL10	<5.0	139.8
TNFα	3.8	15.4
IFNγ	1.5	32.8

*Manufacturer (Genzyme, Boston, MA) detection limits: 3 pg/ml for IL1β, INFγ and TNFα; 4 pg/ml for IL2; 6 pg/ml for IL4; 18 pg/ml for IL6; and 5 pg/ml for IL10.

Before starting immunosuppressive treatment, PF and PB were obtained simultaneously for immunological analysis. Mononuclear cells from both sources were isolated by gradient centrifugation and the frequency of lymphocyte populations 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 plasma. Also, IL1β 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 plasma, is particularly interesting. PF concentrations of IL6 in our patient were substantially higher than those observed in PF from patients with inflammatory and non-inflammatory heart conditions.[5 6] IL6, not only can increase antibody production, but in SLE, B cells have increased reactivity to this cytokine.[7] 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.[8 9]

The decreased pericardial lymphocyte count and fluid characteristics observed here are in agreement with other studies.[10] 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.[11]

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.

LUIS M VILÁ
JOSÉ R RIVERA DEL RÍO
Department of Internal Medicine, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico

LUIS M VILÁ
ZILKA RÍOS
ELIZABETH RIVERA
Department of Microbiology and Immunology, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico

Correspondence to:
Dr L M Vilá, Department of Internal Medicine, Division of Rheumatology, Universidad Central del Caribe School of Medicine, Call Box 60327, Bayamón, Puerto Rico 00960–6032, USA.

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

Anterior uveitis (AU) is the most common form of uveitis,[1–3] and may be produced by different causes. An aetiological diagnosis is commonly established in approximately half of the patients with AU, 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 presenting with associated SA,[4–8] 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.[9 10] 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.

Table 1 Lymphocyte populations in AU patients and controls

	AU patients (n=146)	*Controls (n=31)*	*p Value*
Lymphocytes (no/mm^3)	2425.60 (964.44)	2567.74 (820.72)	NS
CD3 (no/mm^3)	1734.20 (726.67)	1835.64 (586.68)	NS
(%)	71.96 (8.20)	71.27 (4.28)	NS
CD4 (no/mm^3)	1023.91 (489.16)	1219.70 (427.56)	<0.05
(%)	42.56 (9.50)	47.00 (6.13)	<0.05
CD8 (no/mm^3)	702.21 (359.67)	675.90 (243.54)	NS
(%)	29.25 (8.81)	26.72 (6.81)	NS
CD4/CD8	1.70 (0.89)	1.92 (0.78)	NS
CD19 (no/mm^3)	266.87 (227.44)	335.90 (142.35)	NS
(%)	10.81 (5.65)	13.64 (5.09)	<0.05
CD4CD45R+ (no/mm^3)	406.17 (304.18)	657.70 (301.36)	<0.001
(%)	16.70 (9.99)	25.20 (7.76)	<0.001
CD4CD45R- (no/mm^3)	661.53 (338.48)	529.41 (219.04)	<0.05
(%)	27.70 (7.94)	20.77 (6.40)	<0.001
NK (no/mm^3)	300.45 (179.63)	323.80 (182.53)	NS
(%)	13.30 (7.76)	12.81 (5.86)	NS

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

A prospective study was conducted involving 146 patients with active 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 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 1). Patients with IAU had higher percentages of CD4CD45R- (28.46 (7.89)%) than SA patients (23.23 (6.81)%) and the control group (20.77 (6.40)%) (fig 2).

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%[2] and 13%[3] 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,[11] 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. 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 disease, suggesting that these disorders could be attributable to these changes.[12–15] In addition, differences found in the values of CD4CD45R cells between patiens with IAU and SA suggest a different physiopathogenetic mechanism in the development of both

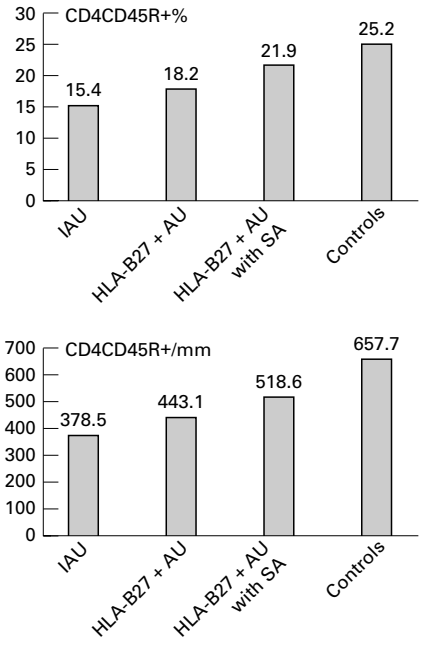

Figure 1 Absolute values of CD4CD45R+ cells. Patients with IAU had absolute values lower than the control group, and percentages lower than those of SA patients (p<0.001). IAU= idiopathic anterior uveitis; AU= anterior uveitis; SA= spondyloarthritis.

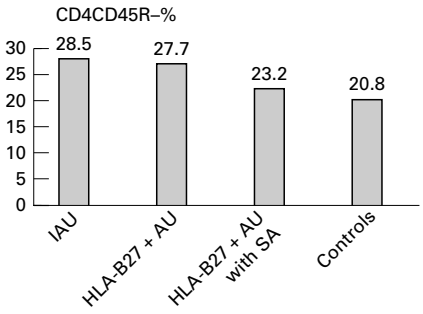

Figure 2 Percentages of CD4CD45R− cells. Patients with IAU had higher percentages than the healthy subjects and SA patients (p<0.001). Abbreviations as in figure 1.

diseases. The immunological features studied, both humoral 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.

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FRANCISCO RIVERA-CÍVICO
JUAN JIMÉNEZ-ALONSO
MARÍA MARTÍN-ARMADA
MARÍA TERESA HERRANZ
JOSÉ CASTRO
FRANCISCO PÉREZ-ALVAREZ
J L DEL ARBOL
Service of Internal Medicine

MANUEL TORIBIO
Service of Ophthalmology

FRANCISCO SAMANIEGO
Service of Clinical Chemistry and Immunology, "Virgen de las Nieves" University Hospital, Granada, Spain

Correspondence to: Dr J Jiménez-Alonso, Jefe del Servicio de Medicina Interna, Hospital General de Especialidades "Virgen de las Nieves" Avda Fuerzas Armadas 2, 18014 Granada, Spain.

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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.[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 diseases (two patients concomitantly developed a T lymphoma and one a myelodiplastic syndrome) suggested that RS3PE syndrome might not be a distinct clinical entity. At that moment 12 patients were asymtomatic and 12 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 symtoms, 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 asymtomatic and without treatment, in contrast nine required treatment, namely corticosteroids (6), gold salts (1), cloroquine (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 polymyalgic symtons at different times. Last but not least one patient developed Raynaud's phenomena, both hands had sclerodactily. A nailfold capillary microscopy showed a decreased number of capillary loops, which were widened, suggesting systemic sclerosis.

Our results suggests that RS3PE syndrome has a good prognosis as more than half of the patients are asymtomatic 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.

MONICA GUMÁ
ENRIQUE CASADO
XAVIER TENA
ALEX OLIVÉ
Rheumatology Section, Hospital Universitari Germans Trias i Pujol, C/ de Canyet s/n, Badalona 08016, Spain

Correspondence to: Dr A Olivé.

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

1 Cantini F, Salvarani C, Olivieri I, Barozzi L, Macchioni L, Niccoli L, *et al.* Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. Ann Rheum Dis 1999;58:230–6
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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,[1] they confirm that RS3PE syndrome should be considered a heterogenous condition associated with different inflammatory rheumatic diseases and also with neoplastic disorders.

In our study[2] 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 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[3] 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.[4]

However, in their retrospective evaluation Olivé *at 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,[2] 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 alternate relapses of bilateral hand pitting oedema or polymyalgic 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.[5] 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.[6]

FABRIZIO CANTINI
2nd Divisione di Medicina, Ospedale di Prato, Italy

CARLO SALVARANI
Servizio di Reumatologia, Azienda Ospedaliera, Acispedale S Maria Nuova, Reggio Emilia, Italy

IGNAZIO OLIVIERI
Servizio di Reumatologia, Ospedale SCarlo, Potenza, Italy

Correspondence to: Dr F Cantini, 2nd Divisione di Medicina, Ospedale di Prato, Piazza Ospedale 1, 59100 Prato, Italy.

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Crystals 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 correlates strongly with radiographic evidence of cartilage degeneration and is associated with larger joint effusions when compared with joints without crystals.[2 3] Whether the presence of apatite crystals is a cause of cartilage damage or an effect of cartilage damage is unclear.[4] Several lines of evidence suggest that apatite crystals cause joint destruction. For example, apatite crystals induce both mitogenesis and prostaglandin synthesis in synovial fibroblasts and chondrocytes in vitro.[5] They also induce matrix metalloprotease (MMP) synthesis and secretion, thus promoting tissue damage.[6 7] The cellular mechanisms whereby apatite crystals induce such responses are currently under investigation. Like many other growth promoting agents, apatite crystals induce a variety of transcription factors such as nuclear factor κB (NF-κB) and activator protein 1 (AP-1).[8] They also induce mitogen activated protein kineses (MAPK) and protein kinase C (PKC).[8 9] Furthermore, such activation is specific as the crystals do not activate protein tyrosine kineses (PTK) or phosphatidylinositol 3-kineses (PI3K).[8] 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 proliferation such as rheumatoid arthritis (RA). However, apatite crystals are rarely found in RA joint fluids.[1] Thus, current data support the potent biological activity of apatite crystals.

On the other hand, the clinical significance of apatite crystals in joint degeneration continues to be questioned. Dieppe and Swan doubt that apatite crystals are of pathogenic significance but they fail to refute or to even reference the vast body of literature that supports the biological activity of apatite crystals.[10] To add to the confusion, they place apatite in a list of pathogenic crystals in the same article. It seems relevant that the importance of balance in the presentation of scientific papers has recently been emphasised.[11]

As noted by Dieppe and Swan, part of the problem is that apatite cannot be readily identified in the same way that monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) can be by polarised light microscopy. Furthermore, the presence of apatite crystals does not change the management of either osteoarthritis (OA) or any other arthropathy in patients at present. Dieppe and Swan 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.[12] As with apatite crystals, levels of cytokines such as interleukin 1 (IL1) or tumour necrosis factor α (TNFα) are not routinely measured in joint fluid from patients with arthritis. After considerable further investigation, however, the roles of IL1 and TNFα in mediating joint degeneration in OA are now considered important.[13] As a consequence of such recognition, Pelletier and coworkers have prevented the development of OA in an experimental model by transfer of the IL1 receptor antagonist gene.[14] We have shown that apatite crystals induce MMP-1 in human OA (HOA) fibroblasts with a potency equivalent to that of IL1 and TNFα in vitro. Furthermore, apatite crystals, IL1 and TNFα act in synergy to increase MMP-1 production by HOA fibroblasts.[15] Efforts continue to discover methods to inhibit the pathogenic effects of IL1 and TNFα. Why not inhibit the effects of apatite crystals also?

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 treatment thus allowing 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

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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 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 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, Univeristy 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.[1] A decrease in mortality risk for rheumatoid arthritis (RA) patients in more recent years would be important, even if 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 observed.

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 have been "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.[2] 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.[2]

JAMES F FRIES
DANIEL A BLOCH
Stanford University, School of Medicine, Palo Alto, California, USA

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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
Department of Rheumatology, Lund University Hospital, Sweden

Table 1

Age group	*Number of patients*	*Expected mortality*	*Observed mortality*
15–19	1	0	0
20–24	3	0	0
25–29	7	0	0
30–34	3	0	0
35–39	15	0	0
40–44	20	1	0
45–49	27	1	2
50–54	34	2	2
55–59	24	3	3
60–64	19	3	2
65–69	16	4	3
70–74	11	4	4
75–79	3	2	2
All	183	20	18