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 be regarded 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.

**Table 1** Lymphocyte phenotypes in patients with SSc and healthy controls

<table>
<thead>
<tr>
<th>Test</th>
<th>n=29</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (%)</td>
<td>71 (9)</td>
<td>0.660 &lt;0.05</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>44 (9)</td>
<td>0.110 &lt;0.05</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>31 (9)</td>
<td>0.914 &gt;0.05</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>3 (9)</td>
<td>1.339 &gt;0.05</td>
</tr>
</tbody>
</table>

Serum sample dilutions were prepared from the patients' sera and normal sera for the controls. The mean percentage values of each cell type were calculated. Student's unpaired t test was used for statistical analysis.

**Results**

In the present study, we found that the percentage of CD3, CD4, and CD8 lymphocytes were significantly different when compared with control group. However, there was no significant difference in the percentage of CD4/CD8 ratios in both groups.

**Discussion**

The results of this study suggest that immune system abnormalities may play a role in the pathogenesis of SSc. Further studies are needed to elucidate the mechanisms involved in the immune system abnormalities in SSc.

**References**


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

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Letters, Matters arising


Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>Lymphocytes (no/mm³)</th>
<th>HLA-B27+ AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (no/mm³)</td>
<td>2425.60 (964.44)</td>
<td>2567.74 (820.72)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (586.68)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (no/mm³)</td>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>1023.91 (489.16)</td>
<td>1077.56 (479.56)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD8 (no/mm³)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(%)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>29.25 (8.81)</td>
<td>26.72 (6.81)</td>
<td>NS</td>
</tr>
<tr>
<td>(%)</td>
<td>1.76 (0.89)</td>
<td>1.92 (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>

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

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 usually 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.** 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 lower percentages (mean (SEM)) of HLA-B27+ AU with IAU than HLA-B27−, (2) HLA-B27+ AU without associated SA, and (3) HLA-B27+ AU with associated SA.

Abbreviations as in figure 1.

Table 1 Absolute values of CD4CD45R+ cells. Patients with IAU had absolute values lesser 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 lesser 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 with synovial 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.

4 Brewerton DA, Cañete J, López-Gómez M, Sampalo A, Mediavilla JD, Especialidades “Virgen de las Nieves” University Hospital, Granada, Spain. 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.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 lymphoproliferative disorder 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.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, 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- 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 polylymphatic 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 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 RSPE 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, Miquel Pons, Isabel Rotés, Ramon Sanmartí, Eduard Kantarzewicz, Miquel Sala, Ivonne Bryesky, Rosa Rosello, Javier Arasa, Marta Larrosa, Genonima Cañete, 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 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 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 spondyloarthropathies. Moreover, patients with a clinical history of cancer were excluded from the study. In their original report these authors performed a retrospective study including all patients with remitting distal extremity swelling with pitting oedema. They recruited also patients not evaluated for spondyloarthropathies, which may be associated with distal extremity swelling with pitting oedema.

However, in their prospective 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 is not associated with other conditions and with a good prognosis exists.

The problem is how to label this clinical picture. As discussed in our article,1 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 RS3PE, distal extremity swelling or pitting oedema or polylymphatic syndromes 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.3

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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1 Olivieri I, Salvarezi C, Cantini F. Remitting symmetrical synovitis: a distinct syndrome or a clinical feature of different infections or rheumatic diseases? J Rheumatol 1997;24:249–52.


8 318:1224–5.


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 it would be “doubtful significance”, and that their identification should have no influence on contemporary 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. A decrease in mortality risk for rheumatoid arthritis (RA) patients in more recent years would be important, as 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 be “expected”. However, using US mortality rates for a population mean aged the same, projected over 10 years, two thirds women, and white, one would expect only 11 deaths using 1996 mortality rates and 12 deaths using 1985 rates, over the 1710 patients years of follow up. While we did not have the age distribution of this RA cohort to calculate precise expectations, these figures should be conservative. Female mortality rates in the US white female popula-

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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 proliferating synovial fibroblasts and chondrocytes in vitro. They also induce matrix metalloproteinase (MMP) 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 induce a variety of transcription factors such as nuclear factor-kappa B (NF-kB) and activator protein 1 (AP-1). They also induce mitogen activated protein kinases (MAPK) and protein kinase C (PKC). Furthermore, such activation is specific as the crystals do not activate protein tyrosine kinases (PTK) or phosphatidylinositol 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 destruction and synovial lining proliferation such as rheumatoid arthritis (RA). However, apatite crystals are rarely found in RA joint fluids. Thus, current data support the potential pathogenicity of apatite crystals.

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 pathogenic significance but they fail to refute the notion to even the vast body of literature that supports the biological activity of apatite crystals. To add to the confusion, they place apatite in a list of pathogenic crystals in the same manner as hydroxyapatite but they fail to refute the notion that the importance of balance in the presentation of scientific papers has recently been emphasised.

As noted by Dieppe and Swan, part of the problem is that apatite cannot be readily iden-

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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.

Authors’ reply

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Table 1

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Expected mortality</th>
<th>Observed mortality</th>
</tr>
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<tr>
<td>15-19</td>
<td>1</td>
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<td>20-24</td>
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<td>30-34</td>
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<td>35-39</td>
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<td>0</td>
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<td>40-44</td>
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<td>0</td>
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<td>45-49</td>
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<td>2</td>
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<td>4</td>
</tr>
<tr>
<td>75-79</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>183</td>
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</table>
Mortality in rheumatoid arthritis patients

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