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, 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 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 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 decline in her renal function. Two years later 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.

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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 might play a part 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 (Epics Profile II) for total T (CD3), T helper (CD4), T suppressor (CD8), B lymphocyte surface marker (CD19), activation marker (CD25) and natural killer cell surface marker NKH1 (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-ScI70 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 ± 2.0 years. Patients were receiving no medication nor had received any immunosuppressive agent for at least three months. Controls were 12 aged sex matched healthy volunteers with an age range from 27–51 years.

Data were compared for significance 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 surface marker CD56+ in lymphocyte phenotypes in SSc. Anti-nuclear antibody was positive in 25 (86.2%) and anti-Sc170 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 ± 2.0 years. Patients were receiving no medication nor had received any immunosuppressive agent for at least three months. Controls were 12 aged sex matched healthy volunteers with an age range from 27–51 years.

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Data were compared for significance Student’s unpaired t test.
Whiteside et al. and Barnett et al. by using the indirect immunofluorescence method, reported that CD8+ suppressor/cytotoxic T cells are decreased in SSc patients. Our findings differ from those of Whiteside and Barnett; we and Degiannis et al. have used the more sensitive flow cytometry method and could not find any differences between the 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. 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. Brunns 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 connective tissue 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+. CD6+ is a homofic adhesion molecule that belongs to the immunoglobin superfamily. NK cells are the main effector cells in 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 pathophysiology 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. In recent studies of pericardial fluid (PF) have been limited to determination of autoantibodies, complements and immune complexes. To further study the pathogenic mechanisms involved in pericarditis we examined 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 polyarthralgia, photosensitivity, oral ulcers, nephritis, non-hemolytic anemia, positive ANA, increased ANA titer, anti-dsDNA and hypocomplementaemia. The patient improved with corticosteroid and intravenous cyclophosphamide treatment. However, on 18 June 1997 he presented with syncope, hypertension (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. Pericardiotome 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 x 10³/mm³). PF cytology showed predominating in PF and type 1 in PB.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Periphera l Blood</th>
<th>Pericardial Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte population (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T CD8+ T cells</td>
<td>57.8</td>
<td>50.0</td>
</tr>
<tr>
<td>CD4+ T cells</td>
<td>17.6</td>
<td>25.0</td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td>34.3</td>
<td>25.0</td>
</tr>
<tr>
<td>NK cells</td>
<td>7.8</td>
<td>8.3</td>
</tr>
<tr>
<td>CD16+</td>
<td>34.3</td>
<td>41.7</td>
</tr>
<tr>
<td>CD56+</td>
<td>34.3</td>
<td>41.7</td>
</tr>
<tr>
<td>CD19+</td>
<td>34.3</td>
<td>41.7</td>
</tr>
<tr>
<td>CD25+</td>
<td>34.3</td>
<td>41.7</td>
</tr>
<tr>
<td>Cytokine concentration (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>3.0</td>
<td>240.0</td>
</tr>
<tr>
<td>IL-1β</td>
<td>&gt;6.0</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>IL-4</td>
<td>&gt;6.0</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>IL-6</td>
<td>16.9</td>
<td>471.0</td>
</tr>
<tr>
<td>IL-10</td>
<td>&lt;50.0</td>
<td>130.0</td>
</tr>
<tr>
<td>TNF-α</td>
<td>3.8</td>
<td>15.4</td>
</tr>
<tr>
<td>IFNγ</td>
<td>1.5</td>
<td>32.8</td>
</tr>
</tbody>
</table>

*Manufactured (Gyneze, Boston, MA) detection limits: 3 pg/ml for IL1β, INFγ and TNFγ; 4 pg/ml for IL2; 6 pg/ml for IL6; 8 pg/ml for IL10.*

The 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 to be present, although mild 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 recurrence of pericardial involvement or SLE exacerbations.

Before starting immunosuppressive treatment, PF and PB were obtained simultaneously for immunological analysis. Mononuclear cells from both samples were separated 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 IL8 with respect to plasma was 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. 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 are in agreement with other studies. The higher frequency of CD4+ T cells and NK cells in PF may 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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7 Ikoni E,CREATE_erratum 6:192–207.

### Table 1 Lymphocyte populations in AU patients and controls

<table>
<thead>
<tr>
<th>Lymphocytes (no/mm³)</th>
<th>AU patients (n=146)</th>
<th>Controls (n=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 (no/mm³) (µµµ)</td>
<td>2425.60 (96.44)</td>
<td>2567.70 (820.72)</td>
<td>NS</td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>1734.20 (726.67)</td>
<td>1835.64 (586.68)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (no/mm³) (µµµ)</td>
<td>71.96 (8.20)</td>
<td>71.27 (4.28)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>1023.91 (489.16)</td>
<td>1057.33 (474.56)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD8 (no/mm³) (µµµ)</td>
<td>42.56 (9.50)</td>
<td>47.00 (6.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>702.21 (359.67)</td>
<td>675.90 (243.54)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CDS</td>
<td>29.25 (8.81)</td>
<td>28.67 (6.81)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4/CDS</td>
<td>1.70 (0.89)</td>
<td>1.69 (0.89)</td>
<td>NS</td>
</tr>
<tr>
<td>CD19 (no/mm³) (µµµ)</td>
<td>266.87 (227.44)</td>
<td>335.90 (142.35)</td>
<td>NS</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>10.81 (5.65)</td>
<td>13.64 (5.09)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD44SR+ (no/mm³)</td>
<td>406.77 (144.18)</td>
<td>657.70 (301.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD44SR+ (%)</td>
<td>16.70 (9.99)</td>
<td>25.20 (7.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD44SR- (no/mm³)</td>
<td>661.53 (338.48)</td>
<td>529.41 (219.04)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD4CD44SR- (%)</td>
<td>27.70 (7.84)</td>
<td>20.77 (6.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4CD45R+ (%)</td>
<td>300.45 (179.63)</td>
<td>323.80 (182.53)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4CD45R+ (%)</td>
<td>13.30 (7.76)</td>
<td>12.81 (5.86)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**AU** = anterior uveitis, **SA** = natural killer cells, **NS** = not significant. Data shown as mean (SEM). 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 CD4CD44SR+ (15.47 (9.49)%), CD4CD44SR− (25.20 (7.76)%) and patients with SA (21.97 (10.16)% (fig 1). Patients with IAU had higher percentages of CD4CD44SR− (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). All patients (19.9%) were classified with IAU without SA; without associated disease. Sero-negative SA are the most frequent entities of lupus erythematosus and rheumatoid arthritis in systemic lupus erythematosus. Lupus 1989;5:110–14.

### Figures

**Figure 1** Absolute values of CD4CD44SR+ cells. Patients with IAU had absolute values lower than the control group, and percentages lower than those of SA patients (p<0.001). **Figure 2** Percentages of CD4CD44SR− cells. Patients with IAU had higher percentages than the healthy subjects and SA patients (p<0.001). Abbreviations as in figure 1.
MATTERS ARISING

RS3PE: six years later

We read with interest the paper by Cantini et al and would like to comment on it.1

In 1992 we performed a retrospective multicentre study of 27 patients with RS3PE. 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 myeloplastic 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 (16 male; 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), clofadroquine (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 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 and a short natural history in the majority 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, Miquel Pons, Isabel Rotés, Raquel Sanmartí, Eduard Kantarēwicz, Miquel Sala, Ivonne Breyresse, Rosa Rosello, Xavier Arasa, Marta Larrosa, Genovima Cañellas, Josep Pujol, Anna Lafont.

Correspondence to: Dr A. Olivé.

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 three 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 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.3

However, in their retrospective evaluation Olivé et al found that 13 of 22 (59%) patients were asymptomatic and drug free over a six year follow up period, confirming that RS3PE not associated with other conditions and with a good prognosis does exist.

The problem is how to label this clinical picture. As discussed in our article, 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 alternative relapses of HLA-B27 positive distal extremity swelling or polymyalgia symptoms further supports our hypothesis. Even those RS3PE patients successively diagnosed as having seronegative rheumatoid arthritis (elderly onset rheumatoid arthritis) do not conflict with our conclusions. Healey described patients who developed episodes of polymyalgia rheumatica and seronegative rheumatoid arthritis at different times during follow up.4

Similar clinical characteristics have been recently described in a population based cohort of patients with giant cell arteritis followed up over a 42 year period. Four of the six patients who fulfilled the criteria for the diagnosis of rheumatoid arthritis during the follow up experienced multiple separate episodes of symmetrical arthritis, proximal symptoms of polymyalgia rheumatica and distal extremity swelling with pitting oedema.5

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Crytal...
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
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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.

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KERSTIN EBERHARDT
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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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<tbody>
<tr>
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<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>20-24</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35-39</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-44</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>27</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>50-54</td>
<td>34</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>55-59</td>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
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<td>19</td>
<td>3</td>
<td>2</td>
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<td>65-69</td>
<td>16</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>70-74</td>
<td>11</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>75-79</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>All</td>
<td>183</td>
<td>20</td>
<td>18</td>
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