MATTERS ARISING

Incidence of RA in people with persistently raised RF

A criticism of the study reported in the Annals1 is that age was not taken into account in the evaluation of the probability of development of rheumatoid arthritis (RA) among symptom free subjects with persistently raised rheumatoid factor (RF). The prevalence of RF can be as high as 14.1% in apparently healthy people aged 67–95 (mean age 81).2 RF is also 3.5 times more common in healthy elderly subjects (aged >65) than in their younger counterparts.1 All these factors may alter the nature of history of arthritis in elderly patients who have RF either in good health or in a non-arthritic presentation of RA.

The latter is exemplified by a patient admitted at the age of 76 with symptomatic, as well as echocardiographically validated rheumatoid pericarditis in the absence of arthritis. Rheumatoid arthritis latent fixation test (RA LFT) was positive with a titre of 1/160, antinuclear factor (ANF) titre was 1/250, and signs of active inflammatory disease included a platelet count of 750 × 10⁹/l, and an erythrocyte sedimentation rate (ESR) of 98 mm/1st h (Westergren). Arthralgia of the hands and wrists developed for the first time two years later (when she was no longer taking steroids), with a subsequent RA LFT titre of 1/80 and an ANF titre of 1/320 about four months after the onset of arthralgia. Radiography showed narrowing of the joint spaces of the hands 12 months later, but there were as yet no erosions at this stage. Erosions were seen in March 1992, approximately two and a half years after the onset of arthralgia, when the RA LFT titre was 1/160, ANF titre 1/160, platelet count 421 × 10⁹/l, ESR 18 mm/1st h. At her most recent attendance, on 2 February 2000, she was still very active, having continued to receive prednisolone (maximum dose 5 mg/d) continuously since 1989. Her only complaint was a little pain in the left thenar eminence and painful heels. RF was now 768 IU/ml, ANF titre 1/320, platelet count 340 × 10⁹/l, ESR 42 mm/1st h. Antibodies against double stranded DNA had not been reported at any stage.

COMMENT

This case shows a remarkable dissociation between arthritic symptoms and levels of RF, perhaps signifying that when the immune status is altered in old age,1 the relation between RF and the natural history of RA might be less clear than it is in younger people.

LETTERS TO THE EDITOR

The HLA-B*2709 subtype in a patient with undifferentiated spondarthritides

In 1998, in this journal, we reported the cases of two B27 positive patients with undifferentiated spondyloarthropathy (sSpA) and showed in a controlled study that the sSpA patients had a higher incidence of >95% of HLA-B27 positive patients with persistent increase of rheumatoid factor (RF) that tends to increase in symptom free elderly people.

However, increased incidence of raised RF in elderly people is not relevant to the findings that we published recently in the Annals.1 We simply observed increased prevalence and incidence of rheumatoid arthritis (RA) in elderly subjects who had one or more RF isotypes persistently raised, usually IgM and IgA, compared with those with a transient increase in RF or persistent increase in only one RF isotype. There was no significant age difference between these two groups of subjects studied.

Dr Jolobe’s case history simply confirms what has already been often reported previously that an increase of RF often precedes clinical manifestation of RA.1 It would have been interesting to know about the RF isotype pattern of his patient. We have noted that the pulmonary manifestation of RA is strongly associated with raised IgA RF.3

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Recently, one of our two patients (No 2) was subtyped and found to be B*2709 positive. As far as we know this subtype has never been found in patients with SpA.

DNA typing of HLA class I alleles was performed using a DNA sample prepared from peripheral blood lymphocytes by the salt-out procedure.1 The class 1 ABC SSP UNITTRAY low resolution kit (Pel-Freez) was used. The primer sets amplify all alleles described by the International Nomenclature Committee of WHO in 1995,1 and in 1997.4 Polymerase chain reaction amplification with sequence-specific primers (PCR-SSP) was used. A control primer pair was present to verify the integrity of the PCR reaction. Molecular typing of B27 variants was performed by a PCR-SSP technique with a DYNAL HLA-B27 kit (DYNAL AS, Oslo, Norway), which identifies all the phenotypically different HLA-B27 alleles, B*2701–11, recognised by the HLA Nomenclature Committee in 1973.1 The typing results for our patients were: HLA-A*0101-02, *3201-02; HLA-B*0801, *2709; HLA-C*0102-03, *0701-07.

To confirm these results HLA-B locus sequence based typing was performed. A unique DNA amplification, encompassing exon 1 to intron 3, and four fluorescent sequencing reactions, covering exon 2 and 3, were used.2 Two intronic amplifiers generated a 1 kb length product useful for direct sequencing. For complete subtyping of the allelic variants PCR-SSP was used. Cycle sequencing reactions allowed the incorporation of a fluorescently labelled deoxyribose terminator for detection on a DNA automated sequencer (ABI PRISM 377, Perkin Elmer). Data processing and allele assignment were performed automatically with specific analysis software that compared the sequencing results against a sequence library and provides individual allele assignment for each sequence. The HLA-B class 1 high resolution typing of our sample was HLA-B*0801:B2709 in agreement with the low resolution typing performed by PCR-SSP.

SpA has a strong association with the HLA-B27 molecule. Studies in humans and transgenic rodents suggest a direct involvement of HLA-B27 in the pathogenesis of the disease. Thirteen subtypes of HLA-B27 (B*01–13) have been described, differing from each other by one or more amino acid changes, mainly in the peptide binding groove. Of these B*2701, 02, 03, 04, 05, 07, 08, and 10 are associated with ankylosing spondylitis (AS). B*2711–13 are rare, which has precluded assessing their putative association with AS. B*2706 is not associated with AS in South East Asia. However some B*2706 positive patients with AS have been reported in China.8 It has been suggested that the B*2706 might protect against SpA. Recently, a study on families in which both B*2706 and B*2709 occurred has suggested that B*2706, although not associated with SpA, does not protect against SpA.9 B*2709 has been found in Sardinia and in continental Italy, where the frequency of HLA-B27 in the general population is around 2%, B*2709 accounts for 25% of HLA-B27 subtypes in Sardinia and 3% in continental Italy.8 D’Amato and coworkers have tested 35 Sardinian patients with AS and 40 Sardinian B27 positive healthy subjects by genomic typing.8 None of the patients with AS were found to be B*2709 positive, in contrast with 25% among the healthy controls. The authors suggested that B*2709 is not 5 Goodwin JS, Searles RP, Tung KSK. Immunological responses of a healthy elderly population. Clin Exp Immunol 1982;48:403–10.
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associated with AS. B*2709 differs from B*2705 by a single substitution (His→Asp) at position 116, which is located in the F pocket of the peptide-binding site. In the opinion of D’Amato and his colleagues the substitution at position 116 might exclude the acceptance of rheumatic peptide from the B*2709.

Our patient was born in the south of Italy, she is B27 positive, and has uSpA with an AS.

substitution at position 116 might exclude the B*2709 by a single substitution (His→Asp) opinion of D’Amato and his colleagues the B*2705 by a single substitution (His→Asp). These observations led the hypothesis that persistent fetal cells in the maternal circulation could mediate a graft-versus-host reaction, resulting in autoimmune disease.

Nelson et al have previously carried out a quantitative assay for male DNA in women with SSc and normal women who had delivered at least one son. They indicated that the mean number of male cell DNA equivalents among controls was 0.38 cells/16 ml whole blood and 11.1 among patients with SSc. In addition, Artlett et al have shown Y chromosome-specific sequences in the DNA extracted from peripheral blood in 32 of 69 women with SSc (46%) as compared with 1 of 25 normal women (4%). They also reported that those allo-cells were T lymphocytes and infiltrated lesion skin. These findings support the hypothesis that fetal microchimerism may contribute to the pathogenesis of SSc. However, this is still controversial because Murata et al have recently reported that there is no significant difference in the presence of fetal DNA in peripheral blood between Japanese patients with SSc and healthy women with non-quantitative assay. Here we report further studies of fetal microchimerism in SSc, SLE, and SS.

We assayed for a specific Y chromosome sequence in the DNA extracted from peripheral blood by a nested polymerase chain reaction (PCR) in 20 patients with SSc, 21 patients with SLE, 18 patients with SS, and 41 healthy volunteers. All patients and healthy volunteers were Asian-Japanese women who had delivered at least one son. The nested PCR was done using the primers DYZ1 positive and negative systemic sclerosis groups

**DYZ1**

<table>
<thead>
<tr>
<th>Positive (n=10)</th>
<th>Negative (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett’s type,</td>
<td>I 3 4 7</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>*p=0.017, systemic sclerosis (SSc) + healthy volunteers.</td>
</tr>
<tr>
<td>Antinuclear factor</td>
<td>10 8 18</td>
</tr>
<tr>
<td>Tissue transglutaminase</td>
<td>4 0 4</td>
</tr>
<tr>
<td>SS-A(Ro)</td>
<td>2 0 3</td>
</tr>
<tr>
<td>SS-B(La)</td>
<td>0 0 0</td>
</tr>
<tr>
<td>RA</td>
<td>3 1 4</td>
</tr>
<tr>
<td>dsDNA</td>
<td>2 0 1</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>0 0 0</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>0 0 0</td>
</tr>
</tbody>
</table>

Based on these findings, we conclude that fetal microchimerism may contribute to the pathogenesis of SSc. However, this is still controversial because Murata et al have recently reported that there is no significant difference in the presence of fetal DNA in peripheral blood between Japanese patients with SSc and healthy women with non-quantitative assay. Here we report further studies of fetal microchimerism in SSc, SLE, and SS. We assayed for a specific Y chromosome sequence in the DNA extracted from peripheral blood by nested PCR in 20 patients with SSc, 21 patients with SLE, 18 patients with SS, and 41 healthy volunteers. All patients and healthy volunteers were Asian-Japanese women who had delivered at least one son. The nested PCR was done using the primers DYZ1 positive and negative systemic sclerosis groups.

| SS A(Ro) | 2 0 3 | 0 0 0 | 0 0 |
| SS-B(La) | 0 0 0 | 0 0 0 | 0 0 |
| RA | 3 1 4 | 0 0 0 | 0 0 |
| dsDNA | 2 0 1 | 0 0 0 | 0 0 |
| Mitochondria | 0 0 0 | 0 0 0 | 0 0 |
| Smooth muscle | 0 0 0 | 0 0 0 | 0 0 |

*PBC = primary biliary cirrhosis.*

**Table 2** Comparison of clinical findings of DYZ1 positive and negative systemic sclerosis groups

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>SSc</th>
<th>SLE</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean (range))</td>
<td>56.1 (44–74)</td>
<td>50.2 (34–82)</td>
<td>54.8 (27–74)</td>
</tr>
<tr>
<td>Duration of illness (years, mean (range))</td>
<td>10.2 (1–26)</td>
<td>11.9 (1–24)</td>
<td>8.7 (1–19)</td>
</tr>
<tr>
<td>DYZ1 positive (No (%))</td>
<td>10/30</td>
<td>0/0</td>
<td>0/33</td>
</tr>
</tbody>
</table>

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Table 1: Period average values of corresponding paraclinical and clinical variables of 16 patients with rheumatoid arthritis followed up prospectively divided into two groups with or without progressive erosive changes on radiographs. Values are medians with range

<table>
<thead>
<tr>
<th>Variable</th>
<th>Erosive progression (n=5)</th>
<th>No erosive progression (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suPAR (ng/l)</td>
<td>1.51 (0.93–2.73)*</td>
<td>1.03 (0.56–2.09)*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>11.4 (6.0–30.1)</td>
<td>11.0 (4.2–29.5)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>24 (15–24)</td>
<td>16 (7–38)</td>
</tr>
<tr>
<td>Tender joints (of 28)</td>
<td>6 (3–20)</td>
<td>4 (0–17)</td>
</tr>
<tr>
<td>Swollen joints (of 28)</td>
<td>4 (1–8)</td>
<td>2 (0–10)</td>
</tr>
</tbody>
</table>

suPAR = soluble urokinase plasminogen activator in plasma; CRP = C reactive protein; ESR = erythrocyte sedimentation rate.

The study group comprised 11 women and five men with a median age of 53.5 years (range 25–80) and a median disease duration of 57 months (range 5–360). Fifteen patients were rheumatoid factor positive and 10 had bony erosions on pre-study radiographs. Antirheumatic treatment included methotrexate (11 patients), hydroxychloroquine (two), sulfasalazine (one), and low dose steroids (eight). Clinical evaluation and measurement of suPAR and disease activity. Plasma suPAR was measured and other clinical and paraclinical variables of disease activity determined in these patients on two or more occasions during a 12 month period. The study included all patients (n=16) for whom comparable radiographs of the wrists and hands were obtainable, and also, when relevant, other symptomatic joints, taken before and after the period of suPAR measurements. The x ray films of participating patients were read independently by a radiologist unaware of the patient’s clinical status and suPAR values. An enzyme linked immunosorbent assay (ELISA) was used to measure suPAR in plasma, as previously described. 1-6

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CORRECTION


The Editor of the Annals regrets that we inadvertently published a reply to Dr Barnsley from Drs Ferrari and Russell that contained some misinformation, and offers his apologies to Dr Barnsley.

Possibly, Drs Ferrari and Russell were confusing Dr Barnsley with someone else. Firstly, Dr Barnsley is a man and not a woman, as they stated. Secondly, Dr Barnsley did not attend the World Whiplash Congress in Vancouver and has not read the transcripts of it and thus could not be, as Drs Ferrari and Russell commented, “well aware of an impressive study presented there”.

(Note: Corrections already appear on the Annals web page (www.annrheumdis.com) and are linked to the original publication.)
Marker of erosive progression in RA

OLE SLOT, NILS BRÜNNER and ROSS W STEPHENS

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doi: 10.1136/ard.59.8.654c

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