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.3 All these factors may alter the natural 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 latency 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 × 10^3/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 × 10^3/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 at this 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

COMMENT


Author’s reply

It is certainly well documented that the incidence of rheumatoid factor (RF) increases with age. However, we are not aware of any study of different RF isotypes in this context, but our own unpublished observation indicates that it is mainly IgM RF that tends to increase in symptom free elderly people.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.4 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 three groups of subjects studied.

Dr Jolobe’s case history certainly confirms what has already been often reported previously that an increase of RF often precedes clinical manifestation of RA.5 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.6

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LETTERS TO THE EDITOR

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

In 1998, in this journal, we reported the cases of two B27 positive patients with undifferentiated spondyloarthropathy (sSpA) and spondarthritis which included the spondylitic arthritis and axial disease.6 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.7 It has been suggested that the B*2706 might protect against SpA. Recently, a study on families in which both B*2704 and B*2706 might protect against SpA. Recently, a study on families in which both B*2704 and B*2706 have suggested that B*2706, although not associated with SpA, does not protect against SpA.

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.9 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

3 Goodwin JS, Searsle RP, Tung KSK. Immuno-

logica responses of a healthy elderly popula-

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 rheumatoid disease with AS that is B27 positive, and has uSpA with an B*2709. The pathogenetic role of Y chromosome is strongly associated with the autoimmunity. The identity of the detected PCR product was confirmed by nucleotide sequencing. The identity of the detected PCR product was confirmed by nucleotide sequencing. The identity of the detected PCR product was confirmed by nucleotide sequencing.

### Y chromosome microchimerism in rheumatoid autoimmune disease

It is well known that some features of chronic graft-versus-host disease (GVHD) resemble those of other rheumatoid autoimmune diseases, such as systemic sclerosis (SSc), Sjögren’s syndrome (SS), and primary biliary cirrhosis (PBC). Furthermore, the development of systemic lupus erythematosus (SLE)-like diseases has been seen in murine models of GVHD. The pathogenesis of rheumatoid autoimmune diseases is still unknown. One possibility that has been suggested is that these diseases are associated with pregnancy because of their strong female predilection and, especially in SSc, a peak incidence after parturition. In 1996 Bianchi et al reported that fetal cells could survive in the maternal circulation for up to 27 years after parturition, a phenomenon termed fetal microchimerism. 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 all-alleles were T lymphocytes and infiltrated lesional 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 (table 2). Our data confirm that male DNA is found more commonly in women with SSc than in normal women. Interestingly, DY1-Z1 was not detected in patients with SLE and there was no significant difference between patients with SS and healthy volunteers. These data suggest that fetal microchimerism may be a phenomenon which is strongly associated with the pathogenicity of SSc and not with the related autoimmune diseases, SLE and SS.

### Table 1 Patients’ characteristics

<table>
<thead>
<tr>
<th>SS</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>
</tr>
<tr>
<td>Duration of illness (years, mean (range))</td>
<td>10.2 (1–26)</td>
<td>11.9 (1–24)</td>
</tr>
</tbody>
</table>

DY1-Z1 positive (No (%))

10% (30) 0 (0) 6 (33) 8 (20)

*PBC = primary biliary cirrhosis.*
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Email: yokumiyabi@med.kawasaki-m.ac.jp


Marker of erosive progression in RA

Urokinase plasminogen activator (uPA) catalyses the formation of the proteolytic enzyme plasmin, which plays a part in tissue degradation and remodelling, and seems to have an important role in the erosive growth of pannus in rheumatoid arthritis (RA). The activity of uPA is localised and intensified by a cell bound receptor (uPAR), expressed by some malignant cells and some inflammatory cell types, including activated synoviocytes in the marginal zone between pannus and cartilage.

The uPAR may become cleaved at the cell surface bound anchor, forming a free soluble receptor (suPAR) which is detectable in steady, low concentrations in healthy controls, but with raised concentrations in patients with disseminated malignant disease.

Recently, in a cross sectional study, we found increased concentrations of suPAR in plasma of patients with RA compared with controls and patients with other types of inflammatory rheumatic disorders. This finding raises the question, whether suPAR might be an easily accessible plasma marker of erosive activity in the synovial joint space in RA.

In a pilot study we followed up outpatients with RA to evaluate the relation between 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 present 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 immunoboss assay (ELISA) was used to measure suPAR in plasma, as previously described.

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 prestudy radiographs. Antirheumatic treatment included methotrexate (11 patients), hydroxychloroquine (two), sulfasalazine (one), and low dose steriods (eight). Clinical evaluation and measurement of suPAR, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were done a median number of three times, and the time interval between radiographs was a median of 22 months.

Table 1 shows the results of the study. We found significantly higher suPAR concentrations (p<0.05) in plasma from those patients with RA whose x-ray findings showed disease progression than in the patients who had no radiographic signs of progression, but the differences in ESR, CRP, and clinical variables were not significantly different.

This study was a pilot study in a clinical setting and conclusions must be drawn cautiously. The main problems, apart from the small number of patients, are, firstly, that in some of the patients prestudy radiographs were one to two years old. However, this would tend to diminish the differences found between the erosive progressive and non-erosive progressive groups as patients in the study period, could be classified as progressive due to previous activity. Secondly, another possible bias, tending to increase the difference in suPAR between the two groups in this study, is that patients with high clinical activity would probably have had more extensive x-ray examinations, increasing the chance of finding new erosions. We did not, however, find a difference in the number of radiographically investigated joints between our two groups of patients.

In conclusion, we find that this study indicates that plasma suPAR may be an easily accessible plasma marker of erosive progression in RA, and further studies on the subject are warranted.

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

<table>
<thead>
<tr>
<th></th>
<th>Erosive progression (n=5)</th>
<th>No erosive progression (n=11)</th>
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<tbody>
<tr>
<td>suPAR (µg/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 (6.1–30.1)</td>
<td>11.0 (4.2–29.5)</td>
</tr>
<tr>
<td>ESR (mm/1st 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>

*<p<0.05, non-parametric Mann-Whitney test.

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

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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 printed in the journal will only appear on the Annals web page (www.annrheumdis.com) and are linked to the original publication.)