Use of anti-citrullinated peptide and anti-RA33 antibodies in distinguishing erosive arthritis in patients with systemic lupus erythematosus and rheumatoid arthritis

R Mediwake, D A Isenberg, G A Schellekens, W J van Venrooij

Abstract

Objectives—Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) can both present with an erosive arthritis with the small joints of the hands affected. Therefore a serological marker would be useful to distinguish between these two diseases at onset. In this study anti-RA33 antibodies, which are found in patients with SLE and RA, and anti-citrullinated peptide antibodies (anti-CCP), which have recently been described as highly specific for RA, were assessed.

Methods—Two hundred and thirty one patients receiving long term follow up for SLE were evaluated for arthritis and classified as erosive and non-erosive disease. Sixty six patients were tested for anti-RA33 and anti-CCP antibodies. All the patients were tested for rheumatoid factor (RF) and HLA-DR4 status.

Results—Ten patients had erosive disease, six of whom were RF positive (60%), and six anti-RA33 positive (60%), whereas only two were anti-CCP positive (20%). Two hundred and twenty one patients had non-erosive disease, 40 of whom were RF positive (18%), 14 were anti-RA33 positive (6%), whereas only one patient was found to be anti-CCP positive (0.5%).

Conclusion—The presence of anti-CCP antibodies may be useful in distinguishing RA from erosive SLE. Anti-RA33 antibodies and RF are unhelpful.

(Ann Rheum Dis 2001;60:67–68)
Table 1 Antibody and HLA-DR4 results in the patients with systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Type of arthritis</th>
<th>RF +ve</th>
<th>Anti-RA33 +ve</th>
<th>Anti-CCP +ve</th>
<th>HLA-DR4 +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deforming major erosions</td>
<td>5/8*</td>
<td>6/8*</td>
<td>1/8</td>
<td>3/8</td>
</tr>
<tr>
<td>Deforming minor erosions</td>
<td>1/2</td>
<td>0/2</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Deforming non-erosions</td>
<td>3/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Non-deforming, non-erosive</td>
<td>40/215</td>
<td>14/50</td>
<td>1/50</td>
<td>56/195</td>
</tr>
</tbody>
</table>

*p<0.01 (compared with the non-deforming, non-erosive group).

Table 2 Antibody characteristics of 10 patients with erosive systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Minor/ Major</th>
<th>RF titre</th>
<th>Anti-RA33 status</th>
<th>Anti-citrulline status</th>
<th>HLA-D status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes/Yes</td>
<td>1/160</td>
<td>Positive</td>
<td>Positive</td>
<td>3, 4</td>
</tr>
<tr>
<td>2</td>
<td>Yes/Yes</td>
<td>1/5120</td>
<td>Positive</td>
<td>Negative</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Yes/Yes</td>
<td>1/80</td>
<td>Negative</td>
<td>Negative</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Yes/Yes</td>
<td>1/840</td>
<td>Positive</td>
<td>Negative</td>
<td>2, 7</td>
</tr>
<tr>
<td>5</td>
<td>Yes/Yes</td>
<td>1/80</td>
<td>Negative</td>
<td>Negative</td>
<td>3, 4</td>
</tr>
<tr>
<td>6</td>
<td>Yes/Yes</td>
<td>1/840</td>
<td>Positive</td>
<td>Negative</td>
<td>3, 4</td>
</tr>
<tr>
<td>7</td>
<td>Yes/Yes</td>
<td>1/840</td>
<td>Positive</td>
<td>Negative</td>
<td>1, 10</td>
</tr>
<tr>
<td>8</td>
<td>Yes/Yes</td>
<td>1/80</td>
<td>Negative</td>
<td>Positive</td>
<td>2, 3</td>
</tr>
<tr>
<td>9</td>
<td>Yes/Yes</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>3, 5</td>
</tr>
<tr>
<td>10</td>
<td>Yes/Yes</td>
<td>1/80</td>
<td>Negative</td>
<td>Positive</td>
<td>1, 4</td>
</tr>
</tbody>
</table>

Methods
Anti-RA33 antibody testing was performed using immunoblotting with soluble nuclear extracts from HeLa cells, as described elsewhere.6 Sixty six patients were tested, 10 of whom had erosive disease. RF was determined by the standard slide latex test; a titre >1/80 was regarded as positive. Anti-CCP antibodies were measured in 66 patients. Anti-CCP antibodies are autoantibodies reactive with a cyclic citrullinated synthetic peptide containing the unusual amino acid, citrulline, as described.6 All HLA typing was performed by the Department of Immunology, Hammersmith Hospital London. In this study the presence or absence of HLA-DRA4 was noted.

Results
Table 1 shows the results obtained. In brief, erosive arthritis was present in 10 of the 231 patients (4%) with SLE. Six of these 10 patients (60%) were RF positive. Six patients (60%) were anti-RA33 positive, and four patients were both RF and anti-RA33 positive. Only two of the 10 patients (20%) were anti-CCP antibody positive. Table 2 shows the distribution of antibodies in these 10 patients. Both RF and anti-RA33 antibodies were often identified in the non-deforming non-erosive group, but anti-CCP antibodies were rarely found.

Discussion
RA and SLE can be difficult to distinguish in the early stages. Joint deformities in patients with SLE may resemble RA despite the far lower incidence of erosions and ligament laxity. It would be desirable to have markers that readily distinguish between these two conditions. From the present data it is clear that patients with SLE who are RF and anti-RA33 antibody positive are statistically significantly more likely to have a deforming major erosive arthritis. Therefore these serological markers do not readily distinguish between patients with RA and those with SLE with erosive arthropathy.

However, anti-CCP antibodies were found in only two of the 10 patients with SLE with erosive disease, and were most uncommon in the other patients with SLE studied. Although the presence of anti-CCP antibodies is not an absolute distinguishing feature between patients with RA and erosive SLE, their presence would appear to indicate the former diagnosis. In contrast, the presence of anti-RA33 antibodies does not distinguish RA from erosive SLE. This finding confirms the observations of Schellekens et al that anti-CCP antibodies are virtually confined to patients with RA. In particular, anti-CCP antibodies may be used as a helpful marker to distinguish RA from SLE. Furthermore, they may prove to be particularly useful in the small group of patients with SLE with erosive disease.

It would now be of interest to undertake a prospective study of patients with early onset synovitis, to compare their RF, anti-RA33, anti-CCP antibodies, and HLA-DR4 status to determine just how effective these markers may be in determining long term outcome in patients whose initial presentation with small joint arthritis may cause some diagnostic uncertainty.

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