Urticaria/arthritis syndrome: report of four B51 positive patients

GIAMPIERO PASERO, IGNAZIO OLIVIERI, GABRIELE GEMIGNANI, AND CLAUDIO VITALI

From the Rheumatic Disease Unit, University of Pisa, Pisa, Italy

SUMMARY  The development of articular manifestations in the course of chronic urticaria or in urticarial vasculitis has been widely reported. It is not completely clear, however, whether common pathogenetic mechanisms are involved in all patients with these clinical features. Four consecutive patients with simultaneous urticarial and articular manifestations, but without an evidence of an immune complex mediated disease, are described. The HLA-B51 antigen was positive in all these patients, suggesting that a common genetic background may be present in some cases of urticaria with articular complaints.

Key words: HLA antigens, Behçet's syndrome, urticarial vasculitis, chronic urticaria.

It is known that articular manifestations may be present in the course of chronic urticaria, Patients developing simultaneously arthritis (or arthralgia) and urticaria, with or without other systemic features, do not appear to be homogeneous from the clinical, immunological, and histopathological points of view, however. Thus an immune complex mediated disease is evident only in about half of the cases, and different degrees of histological damage have been reported to be present in skin biopsy specimens. We recently observed four consecutive patients with chronic urticaria and articular complaints, without any evidence of an immune complex mediated disease, who showed a common genetic background, the HLA-B51 antigen.

Patients and methods

The serological profile of the patients was defined by evaluating the following: total haemolytic complement (CH50) using the method described by Kent and Fife, C3 and C4 fractions using a nephelometric method, C1 esterase inhibitor by radial immuno-diffusion (Behringwerk, Marburg, West Germany), antinuclear antibodies by indirect immunofluorescence on rat liver sections, and antibodies to extractable nuclear antigens by counterimmunoelectrophoresis. Circulating immune complex concentrations were detected by two enzymatic competitive methods using Clq or bovine conglutinin (K) as recognition units. Direct immunofluorescence studies on skin biopsy specimens were carried out in two patients using fluoresceinated sera against immunoglobulins and complement fractions. HLA typing was performed by the method of Terasaki et al.

Case reports

Tables 1 and 2 summarise the main clinical, serological, and histological features of the four patients.

PATIENT 1

In November 1986 a 38 year old man began to complain of evening fever and flares of diffuse urticaria accompanied by facial angio-oedema and swelling or pain, or both, in the hands, wrist, knees, ankles, and feet. The duration of the urticaria/arthritis episodes was between four and 24 hours. Although the situation did not improve he was admitted to our rheumatic unit in March 1987. Table 2 indicates the laboratory results obtained at that time. A skin biopsy in the area of an active urticarial lesion showed a histological picture of leucocytoclastic vasculitis. By contrast, direct immunofluorescence studies were negative for cutaneous deposits of immunoglobulins or complement fractions. HLA typing was A9, A29; B38, B51.
The urticarial flares and arthritis improved only after corticosteroid treatment, and, at present, after a progressive tapering of corticosteroid dosage the patient remains free from symptoms by taking 4 mg of 6-methylprednisolone daily.

**PATIENT 2**
A 35 year old housewife started complaining of nocturnal episodes of urticaria in the arm and leg in April 1983. A year later, evening fever, facial angio-oedema, and arthritis (sometimes arthralgia only) in the hands, wrists, elbows, shoulders, hips, knees, and feet appeared, together with the urticarial episodes. Routine blood examination showed an increase only in the erythrocyte sedimentation rate (90 mm/1st h), together with a positive C reactive protein. A skin biopsy specimen showed the presence of mild perivascular infiltrates of mononuclear cells. The patient recovered after corticosteroid treatment, but in December 1984 she again complained of diffuse urticarial lesions and arthritis in the hands, wrists, knees, and ankles. She was admitted to our rheumatic unit in March 1985. Table 2 lists the data and immunological parameters obtained at that time. Immunofluorescent studies on the skin were negative. A clinical remission was obtained by corticosteroid treatment. In November 1985, however, further acute episodes of urticaria and arthritis occurred, and the patient was again admitted to hospital. The only abnormal laboratory data were erythrocyte sedimentation rate 65 mm/1st h, C reactive protein 156 mg/l, alpha2-globulins 8-7 g/l, and white blood cell count 23.9 x 10^9/l. HLA typing was A2, A30, B51, -;Cw4.

After about one month of corticosteroid treatment she recovered and has been in remission ever since without any treatment.

**PATIENT 3**
A 24 year old man was referred to our rheumatic unit in May 1987 for the evaluation of arthritis and urticaria. He had been well until 1981 when recurrent episodes of a diffuse urticarial rash occurred. In the following months the patient also developed recurrent short (<24 hours) attacks of arthritis in the knees, wrists, ankles, proximal phalangeal joints, and metacarpophalangeal joints of the hands. Acute phase reactants, rheumatoid factor, and antinuclear antibody tests were persistently negative. A diagnosis of palindromic rheumatism was made, and he was treated with tiopronin for the following five years. In August 1986 urticaria reappeared, and in the following months the patient experienced numerous episodes of diffuse urticaria and facial angio-oedema with concurrent short lasting arthritis in the wrists, knees, and ankles. Table 2 shows the results of the laboratory investigation. Skin biopsy on an urticarial lesion showed the presence of mild perivascular infiltrates of mononuclear cells. The patient was effectively treated with 15 mg/day of prednisone, which was subsequently tapered to the current daily dose of 2-5 mg.

**PATIENT 4**
A 28 year old complained of fever, facial angio-oedema in March 1987, and after a few days developed diffuse urticarial lesions, abdominal pain, and contemporary arthralgia without any clear inflammatory feature in the shoulders, elbows, wrists, and knees. Every episode lasted for no more than 24 hours and disappeared after corticosteroid treatment. Table 2 reports the main laboratory investigations. HLA typing was A2, -;B18, B51. After progressive tapering of corticosteroid the patient remained well until November 1987, when a mild flare of urticaria recurred.

**Discussion**

These four consecutive patients presented with a clinical picture characterised by recurrent episodes of urticaria and concomitant arthritis (arthralgia in case 4). Furthermore, certain clinical and immuno-
Table 2  Main laboratory and histological data of the patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>ESR* (mm/h)</th>
<th>CRP* (mg/l)</th>
<th>α2-Globulins (g/l)</th>
<th>WBC* (×10³/l)</th>
<th>Ig (G, A, M, E)</th>
<th>ANA*</th>
<th>Anti-ENA Ab*</th>
<th>Complement profile (C3, C4, CH₅₀)</th>
<th>C1-INH*</th>
<th>CIC*</th>
<th>HLA-B51</th>
<th>Skin histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>&lt;5</td>
<td>8.3</td>
<td>10-9</td>
<td>Increased IgA</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>156</td>
<td>8.7</td>
<td>23-9</td>
<td>Normal</td>
<td>Neg.</td>
<td>Neg.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>45</td>
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<td>11-7</td>
<td>Normal</td>
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<td>Neg.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
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<td>10</td>
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<td>10-9</td>
<td>Normal</td>
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<td>Neg.</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*ESR=erythrocyte sedimentation rate; CRP=C reactive protein; WBC=white blood cell count; ANA=antineuclear antibodies; anti-ENA Ab=antibodies to extractable nuclear antigens; C1-INH=C1 esterase inhibitor; CIC=circulating immune complexes; LV=leucocytoclastic vasculitis; MCI=mononuclear cell infiltrates; ND=not done.
Urticaria/arthritis syndrome

has been reported to be associated with Behçet’s disease in Japan,14 Mediterranean areas,15 16 including Italy,17 but not in the United Kingdom18 or in North America.19 The role of this genetic marker in the pathogenesis or in the clinical behaviour of Behçet’s disease is completely unknown, however. On the other hand, the patients described here did not meet the diagnostic criteria for Behçet’s disease as they did not complain of its typical ocular, mucocutaneous, and neurological manifestations.20 In addition, urticarial lesions have never been described among the different cutaneous features of this disorder.21 The report of this small group of patients with a B51 related urticaria/arthritis syndrome suggests that some genetic analogies may be present. Similar pathogenetic mechanisms could be involved in some patients with both urticarial vasculitis and Behçet’s disease. In addition, the association with the B51 antigen could characterise a separate subset of patients with the urticaria/ arthritis syndrome without any evidence of an immune complex mediated disorder.

References