ARTHRITIS ASSOCIATED WITH MONOCLONAL GAMMAPATHY: CLINICAL CHARACTERISTICS

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SUMMARY
We report nine cases of arthritis associated with a monoclonal gammapathy. Joint involvement was noted simultaneously or after the diagnosis of monoclonal gammapathy was made. The cases had oligoarthritis or polyarthritis mimicking rheumatoid arthritis. However, rheumatoid factor was absent in all patients, and distal interphalangeal joints were involved in two cases and sacroiliitis in one. The plasma cell dyscrasia was a multiple myeloma in two cases and monoclonal gammapathy of undetermined significance in the other patients. The light chain isotype was kappa in eight of our patients. A type I cryoglobulinaemia was associated in four cases; it was detected in the synovial fluid of two of them. We suggest that the occurrence of paraproteinaemia with chronic arthritis is more than a chance association. Moreover, a monoclonal gammapathy should be searched for in patients presenting with atypical seronegative arthritis.

KEY WORDS: Arthritis, Monoclonal gammapathy, Cryoglobulinaemia.

The development of erosive arthritis secondary to amyloidosis might occur during the course of myeloma [1]. However, amyloidosis is a rare event in monoclonal gammapathy of undetermined significance or in stage I myeloma. Twelve cases of erosive arthropathy associated with a monoclonal gammapathy of uncertain significance (MGUS), in the absence of amyloidosis, have been reported previously [2-6]. Arthritis onset occurred after the serological finding of a monoclonal component, and all patients remained negative for the rheumatoid factor.

On the other hand, the incidence of development of a monoclonal gammapathy during the course of rheumatoid arthritis (RA) has been estimated as 3.8% [7]. However, these patients had a long-standing seropositive RA with >10 yr duration before the onset of a monoclonal gammapathy [8].

We report nine cases of inflammatory chronic arthritis associated with monoclonal gammapathy, developing simultaneously or after diagnosis of myeloma in two cases and MGUS in six cases.

MATERIAL AND METHODS
The patients were five females and four males, aged 44–78 yr (mean 64 yr). The mean disease duration was 4.1 yr for the monoclonal gammapathy and 3.3 yr for arthritis. All patients had the onset of arthritis together with or after the diagnosis of monoclonal gammapathy.

The presence of a monoclonal component in the serum was determined using counter-immunoelectrophoresis. Serum concentrations of IgA (normal range 0.9–4.5 g/l), IgG (normal range 8–18 g/l) and IgM (normal range 0.6–2.8 g/l) were measured by nephelometry (Behring). Two patients had multiple myeloma: a stage II myeloma with dorsal spine localization in case 3 and asymptomatic stage I myeloma was diagnosed in case 6. All the other patients had MGUS. Determination of amyloidosis was negative in the four patients who underwent rectal or synovial biopsy.

Blood samples for cryoglobulinaemia were drawn in a warm syringe at 37°C. Cryoprecipitates were isolated after incubation of the serum at 4°C for 5 days. Immunodiffusion studies of the cryoprecipitates were carried out in a 1% agarose medium. Rheumatoid factors were determined by nephelometry (Behring). A value >40 U/ml was considered as positive.

Anteroposterior radiographs of both hands and wrists were taken in a standardized fashion, using single-sided Kodak Ortho emulsion.

RESULTS

Joint involvement
As shown in Table 1, three patients had an asymmetrical oligoarthritis with apparent swelling of the ankle, wrist and metacarpophalangeal joints (MCP). Six patients had symmetrical polyarthritis; the knees, the shoulders, wrist and MCP being the most commonly affected joints. Distal interphalangeal joints (DIP) were involved in two cases and bilateral sacroiliitis in one patient (no. 7). Carpal tunnel syndrome was present in two cases. Rheumatoid nodules or flexor tenosynovitis were not noted.

Extra-articular features were present in three cases: purpura (n = 2), necrotizing vasculitis (n = 2), ischaemic glomerulonephritis (n = 2).

Radiology
X-ray of hand and wrist revealed erosive arthritis in six cases with joint space narrowing and cortical erosion of the MCP, radiocarpal or DIP joints. One
We report nine cases of inflammatory arthritis with an onset together with or after plasma cell dyscrasia was diagnosed. Amyloidosis could be excluded by synovial biopsy or rectal biopsy in four patients where the samples were obtained. An association of a monoclonal gammapathy with RA could not be definitively excluded, although the presentations were atypical. Two patients had DIP joint involvement and patient no. 7 had sacroiliitis, which is rather atypical in RA. Moreover, three patients had vasculitis or glomerulopathy. In all cases, rheumatoid factor was absent. Although an increased incidence of a B-cell dyscrasia has been associated with RA, the monoclonal gammapathy appeared > 10 yr after disease onset [8]. In large follow-up studies, 3.8% of RA cases developed asymptomatic monoclonal gammapathy [7]. However, RA was always typical and seropositive, long standing and antedated the appearance of plasma cell dyscrasia [9, 10].

### DISCUSSION

The table below provides a summary of the cases reported.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gammapathy</th>
<th>Date of onset of arthritis</th>
<th>Diagnosis of M-component</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MGUS</td>
<td>March 1994</td>
<td>Feb. 1989</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>MM</td>
<td>Nov. 1990</td>
<td>March 1990</td>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>4</td>
<td>MGUS</td>
<td>Dec. 1990</td>
<td>Feb. 1990</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>MM</td>
<td>Nov. 1990</td>
<td>Nov. 1990</td>
<td>VMCP</td>
</tr>
<tr>
<td>6</td>
<td>MGUS</td>
<td>March 1990</td>
<td>Feb. 1992</td>
<td>prednisone</td>
</tr>
<tr>
<td>7</td>
<td>MGUS</td>
<td>June 1992</td>
<td>June 1992</td>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>9</td>
<td>MGUS</td>
<td>Nov 1994</td>
<td>- 1991</td>
<td>cyclophosphamide</td>
</tr>
</tbody>
</table>

MGUS: monoclonal gammapathy of undetermined significance; MM: multiple myeloma; VMCP: polychemotherapy with vincristine, cyclophosphamide, melphalan, prednisone.
Arthritis has been related to MGUS in previous case reports [2, 11]. An overview of these cases shows an equal sex ratio and the absence of rheumatoid factor. Only three cases of progressive myeloma have been associated with arthritis developing after the diagnosis of the M-component [2, 3, 5]. No specific heavy chain isotype seems to be associated with arthritis; however, in 89% of our cases the light chain was κ.

In nine reported observations, a type I cryoglobulinaemia could be demonstrated. A long-term follow-up study showed that 5% of patients with essential cryoglobulinaemia had non-erosive arthritis [12]. It has been reported that cryoprecipitable paraproteins may crystallize and precipitate in the synovial tissue [6]. Small crystals have been observed in the synovial fluid of patients with erosive arthopathy associated with myeloma, and the crystals were constituted of the monoclonal component [5, 13]. Moreover, a granulomatous synovitis was described in a case of chronic arthritis associated with type I cryoglobulinaemia [6]. In four of our patients, a cryoglobulin was diagnosed, and we were able to demonstrate its presence in the synovial fluid. In our study, the arthritic process seemed to improve with the treatment of the monoclonal component in most of the patients. These observations further support the hypothesis that the local precipitation of the monoclonal component in the synovium could be responsible for the synovitis [14].

In conclusion, we suggest that the occurrence of paraproteinaemia with chronic arthritis is more than a chance association. However, the pathogenic process that leads to arthritis associated with a monoclonal component is unknown.

REFERENCES