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Monoclonal gammopathy in systemic lupus erythematosus

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We studied the prevalence, type and associated features of monoclonal gammopathy in patients with systemic lupus erythematosus (SLE). Patients included in the University of Toronto Lupus Database with an abnormal band on serum electrophoresis were identified. Monoclonal gammopathy patients were matched with two controls each from the same database by age at SLE diagnosis, sex and disease duration. Of 1083 patients followed at the Lupus Clinic 59 (5.4%) were identified with monoclonal gammopathy. The gammopathies included 32 with IgG, 14 IgM and 12 IgA, one undefined. Nine (15.3%) malignancies were detected in monoclonal gammopathy and 12 (10.1%) in the controls during the entire course of their disease ($P = 0.13$). None had multiple myeloma. There was no difference between patients with monoclonal gammopathy and their controls with respect to disease activity, damage, or dose of steroids. The mean ESR and gammaglobulin levels in the monoclonal gammopathy patients were higher than the controls at last visit. We conclude that monoclonal gammopathy is more frequent in SLE patients than in the general population and has a benign course in patients with SLE. There were no differences in disease manifestations, treatment approaches, or malignancies between SLE patients with and those without monoclonal gammopathy.

Key words: SLE, monoclonal gammopathy, prognosis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology that affects primarily women, often in their reproductive years. It is characterized by profound B-cell hyperactivity, autoantibody formation, and hypergammaglobulinemia. In some patients a monoclonal gammopathy is identified.

The presence of a monoclonal protein in the peripheral blood of individuals without supportive evidence of multiple myeloma, macroglobulinemia, or related disorders is termed monoclonal gammopathy of undetermined significance and was first noted by Waldenstrom.1

Monoclonal gammopathy is characterized by the following findings:2,3 1) the presence of a serum monoclonal protein (M-protein, whether IgA, IgG or IgM), at a concentration $\leq 3$ g/dL; 2) fewer than 10% plasma cells in the bone marrow; 3) no or only small amounts of M-protein in the urine (Bence Jones protein); 4) the absence of lytic bone lesions, anemia, hypercalcaemia and renal insufficiency related to the plasma cell proliferative process;5 stability of the M-protein over time and failure to develop other abnormalities during follow-up;6 no evidence of other B-cell proliferative disorders.

The prevalence of monoclonal gammopathy is estimated to be 1% of all patients older than 25 years, and increases to 3% by age of 70 years.4 Associated non-neoplastic disorders recorded in several large reviews5–7 have included the connective tissue diseases, with rheumatoid arthritis being most common among these. Monoclonal proteins of a heterogeneous type, and quantity, occur in patients with SLE, and although they are not clearly a manifestation of disease activity, their clinical significance is not clear. In a recent study assessing the risk of cancer in patients with SLE, SLE was associated with a greater risk of non-Hodgkin’s lymphoma compared with general population.8 Therefore, in this study our aim was to determine the prevalence, type and associated features of monoclonal gammopathy in patients with SLE.

Patients and methods

The University of Toronto Lupus Clinic has followed lupus patients prospectively since 1970. Patients are
followed at two to six-month intervals according to a standard protocol, which includes serum protein electrophoresis. In those patients who demonstrated evidence of a possible monoclonal gammopathy, further studies were performed including serum and urine immuno-electrophoresis, immuno-quantitation, Bence Jones proteins testing, serum cryoglobulin and cold agglutinin. Bone marrow aspirates and biopsies were infrequently obtained during the course of the follow up period. All patients fulfilled four of the 1982 or 1997 revised American College of Rheumatology (ACR) criteria for the classification of lupus or had three criteria and a positive biopsy for SLE. Table 1 shows the demographic features of the University of Toronto lupus cohort from which the current subjects were identified.

Disease activity is routinely assessed using the Systemic Lupus Erythematosus Activity Index (SLEDAI-2K), a validated index for disease activity in SLE. At each visit clinical and laboratory variables are collected to allow calculation of SLEDAI-2K. Disease activity over time is measured by the adjusted mean SLEDAI-2K (AMS). Accumulated damage is measured using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index.

SLE patients with monoclonal gammopathies were identified from the Lupus Clinic Database. The characterization of the abnormal proteins was determined, as was the quantification of all other immunoglobulins. Skeletal radiographs were reviewed to look for evidence of osteopenia or osteolytic lesions. Patients with monoclonal gammopathies were compared to lupus patients without these changes in a nested case-control study. Each monoclonal gammopathy patient was matched with two SLE patients who did not have monoclonal gammopathy for gender, age at SLE diagnosis, and disease duration.

Statistical analysis

Descriptive statistics were used to describe the University of Toronto Lupus Clinic population as well as the patients with monoclonal gammopathy. Patients with monoclonal gammopathy were compared to their matched controls through the use of Generalized Linear Models (namely, linear regression for continuous variables and logistic regression for categorical variables) where the grouping of matched sets was retained. Rates of death and of malignancies per 100 person-year of disease duration were calculated and compared along with 95% confidence intervals (95% CI).

Results

Of the 1083 patients followed at the Lupus Clinic 58 (5.4%) were identified with monoclonal gammopathy. There were 51 females and eight male patients. Mean age at SLE diagnosis was 35.6 ± 15.1 years. Average disease duration at first abnormal band was 15.0 ± 11.3 years and at last clinic visit 19.8 ± 11.6 years. Thirty-two had IgG, 14 IgM and 12 IgA monoclonal band types. Two of five patients tested for Bence Jones proteins were positive, one kappa band, one lambda. Two patients had skeletal surveys done and both were negative. Only two patients had bone marrow biopsy done to rule out multiple myeloma and both were negative for malignancy (Table 2).

Seven (11.9%) monoclonal gammopathy patients died, compared to 34 (28.8%) in controls (P = 0.002). Time from diagnosis of SLE to death was similar in these patients. Monoclonal gammopathy group 17.1 ± 7.6 years, control group 16.6 ± 12.0 years (Wilcoxon test P = 0.55). Rate of death per 100 person-years was 0.58 (CI 0.28,1.22) in the monoclonal gammopathy group as compared to 1.68 (1.20,2.35) in the controls (P = 0.01). Causes of death included cancer (three), MI (one), infection (two), unknown cause (one) in the monoclonal gammopathy group, and cancer (four), MI (18), infection (11), active SLE (five), unknown (four) in the controls.

Nine (15.3%) malignancies were detected in the monoclonal gammopathy group and 12 (10.1%) in the controls during the entire course of their disease (P = 0.24).

Table 2 Monoclonal gammopathy patients’ characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>59 (5.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age SLE diagnosis (years)</td>
<td>35.6 ± 15.1</td>
</tr>
<tr>
<td>Gender (F : M)</td>
<td>50/9</td>
</tr>
<tr>
<td>Disease duration at monoclonal gammopathy (years)</td>
<td>15 ± 11.3</td>
</tr>
<tr>
<td>Monoclonal type</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>32</td>
</tr>
<tr>
<td>IgM</td>
<td>14</td>
</tr>
<tr>
<td>IgA</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Number patients tested for Bence Jones</td>
<td>5</td>
</tr>
<tr>
<td>Number skeletal survey done</td>
<td>2</td>
</tr>
<tr>
<td>Number bone marrow biopsy done</td>
<td>2</td>
</tr>
<tr>
<td>Progression to multiple myeloma</td>
<td>None</td>
</tr>
</tbody>
</table>
Rate of malignancy per 100 person-years was 0.75 (0.39, 1.44) in the monoclonal gammopathy group and 0.59 (0.34, 1.04) in the controls (P = 0.59). None had multiple myeloma. In the monoclonal gammopathy population these cancers were two breast, one basal cell of the face, one cervical carcinoma in situ, one melanoma, one pancreatic cancer, one case of advanced cervical cancer, one lung cancer, and four cases of unknown primary malignancy. On the other hand, in the control group, there were one cervical-small cell carcinoma in situ, one case of uterine adenocarcinoma, one localized skin cancer, one lung cancer, one small cell carcinoma of the lip and seven cases of unknown primary. Two patients in the monoclonal gammopathy group and one in the control group developed two different cancers. Of note, none of these malignancies was of lymphoproliferative type.

The adjusted mean SLEDAI (AMS) was 5.8 ± 3.7 in the monoclonal gammopathy group and 6.2 ± 5.6 for the controls (P = 0.63). Active renal disease (casts, pyuria, hematuria, proteinuria, WHO class II/III/IV/Vc,d) occurred in 44 (74.6%) of the monoclonal gammopathy group and in 86 (72.9%) of the control group (P = 0.81). Corticosteroids were used by 51 (86.4%) in the monoclonal gammopathy group and 98 (83.1%) (P = 0.55) of the controls. Cumulative dose of steroids was 36.8g ± 42.3 for monoclonal gammopathy and 39.7g ± 36.6 for controls (P = 0.79). Antimalarials were used by 39 (66.1%) patients in monoclonal gammopathy group and 79 (67.0%) (P = 0.91). Immunosuppressive medications were taken by 25 (42.4%) patients in the monoclonal gammopathy group and 59 (50.0%) control patients (P = 0.33) (Table 3). The SLICC/DI at monoclonal gammopathy was 1.73 ± 2.11 for monoclonal gammopathy group and 2.12 ± 2.20 for controls group (P = 0.38). The mean ESR at monoclonal gammopathy was 41.7 ± 26.0 and 29.0 ± 28.9 for controls at last visit (P = 0.04). Gamma globulin level was 15.8 ± 6.1 for monoclonal gammopathy and 12.8 ± 4.7 for controls (P = 0.0007) (Table 3).

### Discussion

Previous studies of immunoglobulins in SLE have concentrated on the alteration in their type and quantity in relation to control values.12 Spontaneous polyclonal B-cell activation, both peripherally and in the bone marrow of individuals with inactive or active SLE, has been demonstrated.13 It has been hypothesized that B cells hyperactivity in SLE favours the escape of abnormal B-cell clones from the normal regulatory mechanisms. An alternative hypothesis is that defective immunological surveillance in SLE patients, predisposing to malignancies in general, promotes the development of MM. This appears to contrast with the rarity of the association in humans.

Plasma cell tumours and lupus nephritis have been documented in animal models.14 But in humans multiple myeloma is very rarely associated with SLE with only eight cases having been reported to date.15–22 SLE also has been described in association with other plasma cell dyscrasias, such as, macroglobulinemia and amyloidosis.23

This is the first study which documents the prevalence of monoclonal gammopathy in a large cohort of SLE patients. In this study, we found that the prevalence of monoclonal gammopathy in SLE patients (5.4%) is higher than general population (1–2%). While we found nine cases of malignancy among patients with monoclonal gammopathy, compared to 12 in the controls we did not detect any cases of multiple myeloma. Moreover there was no difference in the rate of malignancy between monoclonal gammopathy patients and their controls. Mortality was less frequent in patients with monoclonal gammopathy that in the controls, supporting the benign nature of the monoclonal gammopathy in these patients.

There were no differences in disease manifestations, treatment approaches or malignancies between monoclonal gammopathy SLE patients and SLE controls. The presence of monoclonal gammopathy did not correlate with disease activity. As is noted in the general

### Table 3 Main outcomes in monoclonal gammopathy patients and controls

<table>
<thead>
<tr>
<th>Feature</th>
<th>Monoclonal gammopathy</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration mean ± SD</td>
<td>15.0 ± 11.3</td>
<td>15.2 ± 11.1</td>
<td>0.28</td>
</tr>
<tr>
<td>Adjusted mean SLEDAI Mean ± SD</td>
<td>5.8 ± 3.7</td>
<td>6.2 ± 5.6</td>
<td>0.63</td>
</tr>
<tr>
<td>Renal disease n (%)</td>
<td>44 (74.6%)</td>
<td>86 (72.9%)</td>
<td>0.81</td>
</tr>
<tr>
<td>SLICC/ACR DI mean ± SD</td>
<td>1.73 ± 2.11</td>
<td>2.12 ± 2.20</td>
<td>0.38</td>
</tr>
<tr>
<td>Steroid therapy n (%)</td>
<td>51 (86.4%)</td>
<td>98 (83.1%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cumulative steroid dose (g)</td>
<td>36.8 ± 42.3</td>
<td>39.7 ± 36.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Immunosuppressives n (%)</td>
<td>25 (42.4%)</td>
<td>59 (50%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Antimalarials n (%)</td>
<td>39 (66.1%)</td>
<td>79 (67.0%)</td>
<td>0.91</td>
</tr>
<tr>
<td>ESR mean ± SD</td>
<td>41.7 ± 26.0</td>
<td>29.0 ± 28.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Gamma globulin level mean ± SD</td>
<td>15.8 ± 6.1</td>
<td>12.8 ± 4.7</td>
<td>0.0007</td>
</tr>
</tbody>
</table>
population, an unexplained persistently elevated ESR in a patient with lupus should trigger an investigation with serum protein electrophoresis. It has been shown that high dose steroid administration resulted in decreased levels of serum immunoglobulin, which may persist for several months, even after treatment has been stopped. However, we did not find any difference between the two groups in the previous treatment including the dose of steroid.

In summary, monoclonal proteins of a heterogeneous type, quantity, and course occur in patients with SLE more frequently than in general population, and are not clearly a manifestation of disease activity. The course has been benign. None of the monoclonal gammopathy patients progressed to multiple myeloma during the five years of this study. Further investigation of these M proteins may shed light on the pathogenesis of this complex disorder.

Acknowledgement

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References