Prognostic significance of paraproteinaemia in rheumatoid arthritis

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Abstract

The incidence of lymphoma and myeloma is increased in rheumatoid arthritis (RA), though the reasons for this are incompletely understood. The predictive value of monoclonal gammopathy in RA for the later development of lymphoproliferative malignancy was assessed. A serum paraprotein was discovered in 23 patients (14 female) with a median age of 58 years and a median duration of RA of six years. The paraprotein was quantified and further investigations, including a bone marrow examination and skeletal survey, were undertaken to study the possible development of a lymphoproliferative disorder. Secondary Sjögren's syndrome was noted in 12 patients.

The paraprotein was monoclonal in 21 patients and was classed as IgG (12 cases), IgA (six cases), or IgM (three cases). Biclinal paraproteins were seen in two patients. Free light chains were found in the urine of eight patients. Bone marrow abnormalities were found in 13 subjects. The bone marrow was abnormal in four of six patients with an IgA paraprotein, in two of three with an IgM paraprotein but in only five of 12 patients with an IgG paraprotein. Patients were followed up for a median of four years, and five patients with an abnormal bone marrow developed myeloma, of whom three had an IgA λ paraprotein. Two other patients developed non-Hodgkin's lymphoma. Extra-articular bone erosions were seen in four patients, three of whom developed myeloma, but the presence of urinary free light chains was not specific for the development of malignancy. Paraproteinaemia in RA indicates monoclonal B cell proliferation and carries a high risk of malignant transformation.

longitudinal study of patients with paraproteinaemia we attempted to evaluate the risk of lymphoproliferative malignancy and relate it to a variety of easily measured parameters.

Patients and methods

We identified 23 patients with RA⁹ and a serum monoclonal or biclinal paraprotein who had attended a district rheumatology unit serving a population of 800 000 over an eight year period. Their case notes were obtained and the following demographic data recorded: age and sex; date of diagnosis of RA; date of detection of paraprotein by densitometry and concentration of other immunoglobulins at that time. The presence of free light chains in the urine was noted. IgM rheumatoid factor titres and the presence or absence of secondary Sjögren's syndrome were also recorded from the case notes. Sjögren's syndrome was considered present when sicca symptoms were supported by the finding of an abnormal Schirmer test with less than 10 mm wetting bilaterally over five minutes. Skeletal surveys were carried out on all patients, and in those found to have extra-articular erosions an isotope bone scan was undertaken.

All patients had undergone bone marrow aspiration and trephination, and samples were independently reviewed by one of us (GB) without knowledge of the report previously issued by the attending haematologist. The following details were recorded: overall cellularity, plasma cell morphology, percentage, and distribution on trephination. When the reports differed significantly a second observer was asked to examine the slides without reference to previous reports.

Although most patients had been followed up on a regular basis in the rheumatology department, all patients were recalled to the outpatient clinic and sequential changes in paraprotein and immunoglobulin concentrations were recorded from haematology record sheets. Determinations of autoantibody titres and immunoglobulin concentrations were specifically repeated at this visit. Bone marrow examination was repeated only in patients with a strong clinical indication. All treatment received since detection of the paraprotein was recorded.

Statistical comparisons between those paraprotein concentrations found initially and those found at follow up were made with Student's unpaired *t* test, whereas the Wilcoxon rank test was used to compare paraprotein concentrations between subgroups.

A relation between rheumatoid arthritis (RA) and myeloma was proposed by Galli and Chiti in 1955¹ and supported by Goldenberg *et al.*² Firm evidence that RA is associated with an excess risk of both myeloma and lymphoma was first obtained from a large population study in Finland in 1982.³ Confirmation of the increased risks of myeloma and lymphoma in RA have recently been obtained from smaller studies with clearer diagnostic criteria.^{4,5} There is evidence that the risk of these malignancies relates to the duration of RA,⁶ but there is little published information on other risk factors. In particular, the possible relevance of monoclonal gammopathy to malignancy in rheumatic disease has only recently been discussed.^{7,8} In this

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Table 1 Demographic details of 23 patients with rheumatoid arthritis (RA) and a serum paraprotein at follow up

Patient No	Age at onset of RA (years)	Duration of RA (years)	Duration of paraprotein (years)
1	42	8	8
2	52	16	2
3	59	5	5
4	49	1	1
5	62	5	4
6	61	13	7
7	43	35	5
8	64	7	4
9	71	5	5
10	58	10	7
11	29	35	2
12	52	7	6
13	43	14	4
14	71	5	1
15	61	5	1
16	43	19	9
17	56	9	7
18	18	38	1
19	42	16	2
20	56	21	3
21	52	3	3
22	48	7	5
23	50	18	1
Median (range)	52 (18–71)	10 (1–38)	4 (1–9)

Results

Fourteen of our 23 patients were female, giving a female:male ratio of about 1.5:1. The median age of the group at discovery of the paraprotein was 58 years (range 41 to 75) and the median duration of RA at this time was six years (range 0 to 37). Diagnosis of RA and discovery of paraproteinaemia were synchronous in five patients, but in none was the paraprotein found before the onset of joint symptoms. Table 1 provides individual demographic details, including the duration of follow up.

PARAPROTEIN

Initial assessment showed the paraprotein was monoclonal in 21 patients and biclonal in two. It was typed as IgG in 12 subjects (10 $\times$:2 λ), IgA in six (1 $\times$:5 λ), and IgM in three (2 $\times$:1 λ). The two patients with a biclonal paraprotein both had IgA λ bands, together with an IgG κ in one case and an IgM κ in the other. The median concentration of paraprotein was 9.0 g/l (range 2.3–33.0) and did not differ significantly between immunoglobulin subclasses. Immune paresis with depression of the other immunoglobulin concentrations was seen at this stage in two patients, whereas a polyclonal increase in immunoglobulins was evident in four subjects with secondary Sjögren's syndrome (table 2).

Free light chains were found in the urine of eight patients. Four had free κ chains, three had λ chains, while one patient with a biclonal paraprotein had both. Twenty patients were

seropositive for IgM rheumatoid factor and three patients were seronegative at the time the paraprotein was detected. Titres of rheumatoid factor ranged from 1/160 to 1/1280 and 12 patients had secondary Sjögren's syndrome. Erosive joint disease was present in all seropositive patients and two seronegative patients. Extra-articular erosions were seen in four patients on the skeletal survey, of whom three were seropositive. Bony lysis was present in the humeri in three of these patients and in the femora in the remaining patient. Isotope bone scans were positive in each of these four patients.

BONE MARROW

Bone marrow examination showed significant abnormalities in 13 patients. These usually included an increase in overall cellularity with an expansion of the plasma cell population. More specific features included the presence of binucleate, blastic, or lymphoplasmacytoid plasma cells. Abnormal plasma cell distribution was also seen with focal and paratrabecular aggregates. In one patient direct immunofluorescence was used to confirm the monoclonality of plasma cells. The independent review was significantly different from the initial report in three patients and thus the opinion of the second observer was sought. This concurred with the findings of the independent reviewer in each case.

An abnormal bone marrow was found in four of six patients with an IgA paraprotein and in two of three subjects with an IgM paraprotein. Five of 12 patients with an IgG paraprotein and both the patients with a biclonal paraprotein were also found to have an abnormal marrow. The risk of an abnormal bone marrow was no greater among the patients with secondary Sjögren's syndrome nor among those with urinary free light chain excretion. Furthermore, in only two of the five patients with both secondary Sjögren's syndrome and free light chain excretion was the bone marrow found to be abnormal.

FOLLOW UP

All 23 patients were reviewed at a median of four years (range 1–9) after the initial report of their paraproteinaemia. Table 3 shows that median concentrations of paraprotein had increased from their initial values in all immunoglobulin subclasses, though this increase was significant only for IgA paraprotein ($p < 0.05$). Overall, the median paraprotein concentration rose slightly to 10.9 g/l (range 0–60) but was no longer detectable in two patients with low concentrations of paraprotein initially. Paraprotein concentrations were stable in 17 patients and had risen by more than 5 g/l in only four subjects. Immune paresis had developed in two of these patients during follow up. Titres of rheumatoid factor did not alter significantly during the follow up period, and none of the three seronegative patients became seropositive.

Five of the 23 patients reviewed had developed myeloma,¹⁰ of whom three had an IgA λ mono-

Table 2 Initial paraprotein concentrations in 23 patients with rheumatoid arthritis, grouped by paraprotein subclass

Paraprotein	κ : λ Ratio	Paraprotein median concentration (range) (g/l)	Other immunoglobulins*
IgG (n=12)	10:2	10.8 (2.3–33.0)	Normal 8; ↑ 2; ↓ 2.
IgA (n=6)	1:5	7.6 (3.4–12.4)	Normal 3; ↑ 0; ↓ 3.
IgM (n=3)	2:1	8.2 (3.4–18.0)	Normal 2; ↑ 1; ↓ 0.
Biclonal (n=2)			Normal 1; ↑ 1; ↓ 0.

* ↑ = increased; ↓ = decreased.

Table 3 Follow up data in 23 patients with rheumatoid arthritis and a paraprotein, grouped by paraprotein subclass

Paraprotein	Paraprotein median concentration (range) (g/l)	Abnormal marrow No (%)	Myeloma No (%)	Lymphoma No (%)
IgG (n=12)	11.3 (0-60.0)	5 (42)	2 (17)	1 (8)
IgA (n=6)	12.4 (0-16.6)	4 (67)	3 (50)	0
IgM (n=3)	10.0 (5.2-18.4)	2 (67)	0	1 (33)
Biclonal (n=2)		2 (100)	0	0

clonal paraprotein. Two further patients had histologically proved non-Hodgkin's lymphoma at review. Five of these seven patients were male. No patient developed both these malignancies, and no other neoplasms developed during the follow up period. Three of four patients with immune paresis developed myeloma, whereas none of the patients with a polyclonal rise in immunoglobulins developed malignancy. Table 3 shows the relation between outcome and paraprotein type. Bone marrow examinations were repeated in only four patients. This was performed to assess possible progression towards lymphoproliferative change in three patients with high concentrations of paraprotein, and showed features of myeloma in one of these. In one patient with previously established myeloma a repeat bone marrow examination was done to assess the response to treatment.

Both patients with non-Hodgkin's lymphoma had secondary Sjögren's syndrome, which was present in only two of the patients with myeloma. Two patients with myeloma but neither of those with non-Hodgkin's lymphoma had free urinary light chain excretion. Three of four patients with extra-articular erosions developed myeloma. The duration of RA was at least 12 years in all patients who developed malignancy, with the one exception having developed myeloma six years after the onset of RA.

TREATMENT

All patients had received non-steroidal anti-inflammatory drugs at some stage. Four patients had been given second line treatment with intramuscular gold and treatment with penicillamine had been started in one. Three patients had received oral steroids. No patient had been treated with cytotoxic drugs for RA, though one had received chlorambucil for thrombocytopenic purpura.

Both patients with non-Hodgkin's lymphoma were treated with radiotherapy and one underwent surgery to debulk tumour mass. One patient died, but the other was well at follow up with no evidence of recurrent tumour. Three patients with myeloma underwent treatment with cyclical melphalan and prednisolone. One patient remains anaemic and unwell four years after diagnosis, but the other two are presently well one and five years after treatment. A fourth patient is about to start treatment, and treatment has been unnecessary in one virtually asymptomatic woman.

Discussion

Our study suggests that monoclonal gammopathy in RA carries a high risk for the development of later lymphoproliferative malignancy. Mortality is increased in patients with RA,¹¹⁻¹³ but there has been only limited evidence that lymphoproliferative disorders contribute significantly to this excess.^{14 15} Indeed, in a survey of patients with lymphoproliferative malignancy Miller was unable to show an excess of patients with RA,¹⁶ and Owen *et al* could find no increase in neoplasia of the lymphoreticular system in a review of almost 200 patients with RA.¹⁷ Larger surveys of patients with reticuloses¹⁸ or RA,¹⁹ however, have shown firm evidence of an association between lymphoma and RA. This is consistent with the situation in Sjögren's syndrome where the relative risk of developing non-Hodgkin's lymphoma has been estimated to be as high as 44.²⁰

Less attention has been paid to a possible association between RA and myeloma. In two series reported 20 years ago, however, six cases of myeloma occurred in a group of 16 patients with RA and paraproteinaemia,²¹ and a further five patients with RA and a paraprotein developed myeloma.²² Although prognostic factors were not discussed, IgA and IgM paraproteins occurred almost as often as IgG paraproteins in these patients. Paraproteinaemia occurs in about 1% of patients under the age of 60 and thereafter its incidence rises sharply with age.²³ Estimates for the risk of evolution into a malignant disorder vary widely from 0.5% in patients with a low concentration of a stable paraprotein²⁴ to as many as 28% of elderly patients over a 10 year period.²⁵

In 296 patients with monoclonal gammopathy Waldenström found three patients with RA.²⁶ A further three patients with RA were reported in a series of 150 cases of paraproteinaemia,²⁷ giving an overall prevalence of 1.3%. In two large series a total of eight cases of monoclonal gammopathy were found among 640 patients with seropositive RA,²¹ giving a prevalence of 1.25%. As both RA and paraproteinaemia occur in about 1% of the population the association between the two conditions at best seems to be slight. The significance of monoclonal gammopathy in RA differs from that in the normal population, however. We suggest that the development of lymphoproliferative disorders in some patients with RA may be predicted by the presence of monoclonal paraprotein which, although not found in gross excess in a rheumatoid population, seems to carry a much higher risk of malignant transformation in patients with RA than in the population at large. The increased risk of lymphoma and myeloma in RA may be due to chronic immune stimulation and the associated B lymphocyte activation,²⁸ and rheumatoid lymph nodes are known to be a major site of this B cell driven activity.²⁹

The class of paraprotein present may be of some prognostic value. Previous studies have reported more IgA and less IgG paraproteins in patients with RA than found in the general population.^{21 22 30} Our findings are similar, and suggest that the risk of myeloma may be greater in those patients with a monoclonal IgAλ

paraprotein. The $\kappa:\lambda$ light chain ratio in our patients with an IgA paraprotein was 0.2, which contrasts with the ratio of 1.3 reported in a large series of patients with monoclonal gammopathy without RA.³⁰ The reported $\kappa:\lambda$ ratios in the other paraprotein types were similar to those found in our study. Other well recognised factors, such as a high concentration of paraprotein and the presence of immune paresis, were also predictive of malignancy in our patients.

The presence of urinary free light chains has been proposed as a marker of malignancy in patients with primary Sjögren's syndrome.^{31, 32} We were unable to show a relation between free light chain excretion and malignant transformation in our patients with secondary Sjögren's syndrome. Both our patients who developed lymphoma had associated secondary Sjögren's syndrome, however, and the increased risk of lymphoma in Sjögren's syndrome is unaffected by the presence of associated connective tissue disease.²⁰ Amyloidosis may also complicate longstanding RA and can be associated with the production of paraprotein. No evidence of amyloid was found in any of our patients, though it was not actively sought unless felt to be of potential clinical relevance.

Bone marrow examinations were abnormal in over half our patients. Abnormality can be difficult to define in patients with RA as a reactive plasmacytosis is commonly associated with active joint disease, but was based more on atypical morphology and distribution of plasma cells than on their numbers alone. Certain features, such as focal aggregation or paratrabecular distribution of plasma cells, suggest the development of malignancy,³³ but strict criteria for the diagnosis of myeloma were met in only five patients during the follow up period.¹⁰ The bone marrow was abnormal in both patients who later developed lymphoma. Six patients with excessive or abnormal plasma cells have not developed lymphoproliferative disease, and this group includes both patients with biclonal gammopathy. One patient with an IgG paraprotein has now developed immune paresis, however, and another with an IgM paraprotein has findings suggestive of early Waldenström's macroglobulinaemia, so clearly this borderline group remains a cause for concern and later progression to lymphoproliferative malignancy remains a strong possibility.

Only eight patients had received treatment with second line agents or oral steroids, and there is no evidence that these drugs predispose to malignancy. One other patient had received cytotoxic drugs. There is growing concern that the use of such agents in patients with severe RA may increase the risk of later lymphoma,³⁴ though this patient has remained well. A single death has occurred among our seven patients with lymphoproliferative disease, but it is too early to speculate on the long term prognosis.

Our study offers evidence that the development of paraproteinaemia in patients with RA is related more to disease severity than to duration. The median age of our group when a paraprotein was first detected was 58 years and the average

duration of RA at this stage was six years, while most of our patients had erosive disease and were seropositive. We suggest that paraproteinaemia occurring in patients with RA should be promptly investigated with a skeletal survey and a bone marrow examination. Elderly men with severe disease are most at risk of developing a lymphoproliferative disorder, and the presence of an IgA paraprotein may indicate a special risk of myeloma. All patients with morphological abnormalities on bone marrow examination should be followed up six months later with paraprotein measurement and immunoglobulin estimation. A rise of 5 g/l in paraprotein concentration over one year or the development of immune paresis should prompt reinvestigation as the response to treatment of lymphoproliferative disease seems to be at least as good as that obtained in patients without RA.

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