Annals of the Rheumatic Diseases, 1984; **43**, 132–135

Lymphoproliferative malignancy in rheumatoid arthritis: a study of 20 cases

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SUMMARY A series of 20 patients with definite or classical rheumatoid arthritis who subsequently developed a lymphoproliferative malignancy are described. The mean time between the onset of the 2 diseases was 13·2 years. A wide range of types of non-Hodgkin's lymphoma and Hodgkin's disease were found; there were no unusual histological features in the lymphomas. Although many of the patients had had gold, penicillamine, and other second-line drugs, none of them had received cytotoxic drugs, and there was no evidence that therapy was a cause of their malignancies. The likely cause of the association is a predisposition to both diseases.

Various reports have suggested there is a relationship between connective tissue disorders and lymphoproliferative malignancy (LPM).[1-8] This is particularly the case in rheumatoid arthritis (RA), and we have confirmed this association in our previous paper.[9] However, morbidity and mortality studies often fail to define precisely the relationship between individuals and their diseases, including the temporal interrelations, the severity of RA in cases developing malignancy, and any possible effects of drug therapy. To investigate in detail these relationships we have reviewed 20 patients with RA who subsequently developed LPM. This review has included re-examination and reclassification of the histopathological specimens and a detailed examination of therapy given for RA. In addition bone marrow studies have been performed on a series of 9 other patients who had RA and marked hypergammaglobulinaemia in an attempt to detect a premalignant stage of restricted lymphoproliferation.

Patients and methods

The patients in this study came from 3 sources: (1) 9 patients who subsequently developed LPM from a series of 489 consecutive patients with RA seen by the Rheumatology Department, Queen Elizabeth Hospital, Birmingham between 1964 and 1978; (2) 5 patients who had been attending the Royal National Hospital for Rheumatic Diseases, Bath, for varying lengths of time with RA, and who developed LPM between August 1977 and December 1978; these were the only known cases of RA with LPM seen during this period. (3) 6 patients who presented to the Medical Oncology Clinic, Guy's Hospital, with lymphomas between May 1976 and April 1981, and were found to have a documented preceding history of RA; they were the only known cases of RA with LPM seen during this period whose records could be consulted.

The Birmingham cases are from a defined group of patients with RA (see Prior *et al.*[9]) and can be considered a representive sample; the other cases have been ascertained in different ways and as such are selected groups. All 20 patients had classical or definite RA. Their records were examined to obtain the following information: date of onset of RA, rheumatoid factor status, treatment of RA, The American Rheumatism Association functional class[10] at the time of presentation of LPM, date of diagnosis of LPM, and histological diagnosis. Where necessary the histology was reviewed by one author (E.L.J.) to bring it in line with the Rye classification for Hodgkin's disease[11] and the Kiel classification for non-Hodgkin's lymphoma.[12]

An attempt was made to detect an intermediate

Accepted for publication 5 May 1983.
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stage of restricted clone development. Nine patients (not included in the 20 above) with classical RA, marked hyperglobulinaemia (more than twice the upper limit of normal for the laboratory using radial immunodiffusion), and no evidence of malignancy were studied. Bone marrow immunofluorescence was performed with monospecific antisera to the light chains to determine the κ/λ ratios in the plasma cells obtained in aspirates after sternal puncture. One would expect the κ/λ ratio to be altered in oligoclonal or monoclonal gammopathy. Immunoelectrophoresis was performed with monospecific antisera to immunoglobulins G, A, and M, and Bence Jones protein was measured in concurrent specimens of serum and urine.

Results

Of the 20 patients with RA and LPM 7 were males and 13 female. The mean age of onset of RA was 49·4 years (range 29–67) and the mean age at diagnosis of LPM was 62·1 years (range 40–74). The mean time interval between the 2 diseases was 13·2 years (range 2–25). All patients had chronic established RA. Full details are shown in Table 1. The shortest interval between diseases was shown by the only patient who had Sjögren's syndrome (case 1). Patient 12, however, presented with a lymphoma in the parotid gland. Table 2 shows the rheumatoid factor status and the American Rheumatism Association functional class at the time of diagnosis of LPM: 80% were seropositive, and they showed variation in functional class from grade I to III. The extra-articular findings are also shown. As a group these patients did not all have particularly severe RA nor were they all seropositive. Instead they are a group of patients with RA of widely differing severity developing LPM at different stages in the course of their RA. All patients had received nonsteroidal anti-inflammatory drugs. Of the 13 patients who had received further therapy 8 had received gold, 4 chloroquine, 3 penicillamine, and 6 corticosteroids. These drugs were given for varying periods of time ranging from months to years. But they were used no more extensively in cases with LPM than other patients with RA at each centre. For example, of the 9 Birmingham cases 4 (44%) had received gold compared with 34·2% of the overall Birmingham series,[9] and 1 (11%) had received steroids compared with 50·7% of the series. The use of chloroquine and penicil-

Table 1 *Details of lymphoproliferative malignancies*

Case	*Source*	*Sex*	*Age at onset RA (years)*	*Age at diagnosis LPM (years)*	*Interval (years)*	*Histological diagnosis*	
1	G	F	58	60	2	HD	Lymphocyte depletion (high-grade malignancy)
2	B	M	60	63	3	NHL	ML lymphocytic (low-grade malignancy)
3	B	M	61	65	4	NHL	ML lymphoblastic (high-grade malignancy)
4	Ba	F	67	71	4	*NHL	ML histiocytic (high-grade malignancy)
5	Ba	F	73	77	4	NHL	ML lymphoplasmacytic (Waldenström's type; low-grade malignancy)
6	Ba	M	47	54	7	NHL	ML lymphocytic (low-grade malignancy)
7	B	F	57	65	8	CLL	Low-grade malignancy
8	B	M	42	51	9	CLL	Low-grade malignancy
9	B	M	47	57	10	HD	Mixed cellularity (high-grade malignancy)
10	G	F	29	40	11	HD	Mixed cellularity (high-grade malignancy)
11	B	M	46	61	15	NHL	ML immunoblastic (high-grade malignancy)
12	B	F	52	68	16	NHL	ML centroblastic (high-grade malignancy)
13	B	F	48	66	18	NHL	ML centroblastic (high grade malignancy)
14	B	F	54	72	18	NHL	ML immunoglastic (high-grade malignancy)
15	G	M	29	49	20	HD	Nodular sclerosis (low-grade malignancy)
16	Ba	F	54	74	20	NHL	ML lymphoplasmacytic (Waldenström's type; low-grade malignancy)
17	G	F	46	58	22	HD	Mixed cellularity (high-grade malignancy)
18	Ba	F	39	63	24	NHL	ML centrocytic/centroblastic, follicular (low-grade malignancy)
19	G	F	32	56	24	NHL	ML centroblastic (high grade malignancy)
20	G	F	36	61	25	NHL	ML centrocytic/centroblastic, diffuse (low-grade malignancy)

* Not reviewed by E.L.J.
Ba = Bath; B = Birmingham; HD = Hodgkin's disease; NHL = non-Hodgkin lymphoma; CLL = chronic lymphocytic leukaemia; G = Guys; ML = Malignant lymphoma.

Table 2 *Rheumatoid factor, functional class, treatment and associated findings*

Case	*RF*	*Functional class*	*Treatment*	*Associated findings*
1	+	II	P	Sjögren's syndrome
2	+	II	—	Thyroidectomy
3	+	III	GS	
4	+	III	—	
5	+	III	G	
6	+	III	—	Pericarditis
7	+	II	—	Amyloidosis, macroglobulinaemia
8	+	II	G	
9	+	I	GC	
10	−	II	GPCS	
11	+	II	—	
12	−	III	—	
13	−	II	—	
14	+	II	G	
15	+	II	C	
16	+	III	PS	Digital vasculitis
17	+	II	S	
18	+	III	G	
19	+	III	GS	Bowen's disease
20	−	III	CS	Irradiation of rodent ulcer

G=gold; P=penicillamine; C=chloroquine; S=steroids.

lamine also seemed similar in cases with LPM and in cases of RA without LPM. Only one patient had received more than 2 disease-modifying drugs. None had received immunosupressants. One patient (case 20) had received radiotherapy to a rodent ulcer over the zygoma. Her lymphoma developed 25 years later and presented as generalised lymphadenopathy.

The results of the bone marrow immunofluorescence studies showed that the 9 patients with RA and marked hypergammaglobulinaemia had normal κ/λ ratios. Two patients had reduction of other immunoglobulins but did not develop Bence Jones proteinuria or a monoclonal gammopathy. Attempts to demonstrate a premalignant phase in these patients have therefore been unsuccessful.

Discussion

Various hypotheses may explain an association between LPM and autoimmune disease. These include *(a)* proliferation of a forbidden clone of lymphocytes producing both diseases; *(b)* chronic immune stimulation causing malignant transformation of B cell lines; *(c)* susceptibility in both diseases due to genetic predisposition or a single causative agent such as a virus; *(d)* treatment of the autoimmune disease leading to LPM. The relatively long period between the onsets of RA and LPM in many of our cases, which was also seen by Banks *et al.*[8] makes the first hypothesis unlikely.[13] It may also explain the failure of some mortality studies to detect an excess of LPM in RA.[14-16]

Although no lymphocyte surface marker studies were performed in our patients, 12 of the 13 cases of NHL belonged to the B-cell series by morphological criteria. This and the long period between diseases both point to chronic immune stimulation being a possible cause of malignant transformation in antibody-producing plasma cells or B-cell precursors. B-cell derived LPM also have been described in Sjögren's syndrome.[17] However, in patients with RA and severe hypergammaglobulinaemia the κ/λ ratio of plasma cells in the bone marrow was normal, and this is against the second hypothesis.

On balance we consider the most likely cause of an association is a predisposition to both diseases. Our reasons are, firstly, that LPM can develop at various stages of RA (from 2 to 25 years), in both seropositive and seronegative cases, and in patients with RA showing considerable variation in severity. Secondly, many patients may have chronic immune stimulation in RA without developing LPM and despite marked hypergammaglobulinaemia do not develop evidence of restricted clone formation. Thirdly, there is little good evidence to implicate drug therapy. However, whether this is a genetic or environmental predisposition remains to be elucidated.

The risks of therapy causing LPM in RA and other autoimmune diseases are the subject of considerable debate.[18-20] This is particularly the case when cytotoxic drugs are used, though penicillamine has also been implicated. We found no positive evidence to implicate therapy as a cause of any of the LPM we studied. None of our cases had been given cytotoxic drugs. We suggest that any increased risk of LPM which may be attributed to the use of cytotoxic drugs in treating RA must be subjected to a very critical evaluation, and in many cases other causes may be involved. Since a variety of prospective studies of the risks of cytotoxic drugs in treating RA and other connective tissue diseases are in progress, and this risk is considered an especial hazard of this effective form of therapy, we suggest that the fact that none of our cases had these drugs is of interest and significance. It is still possible that other drugs may play a part. Only 3 of our patients had had penicillamine, which is used widely at the centres we have studied, and it seems unwarranted to implicate this. Nevertheless, since multiple therapies are used in RA, our study cannot absolve drugs as a cause of part of the excess of LPM.

We thank the Endowment Fund of the Central Birmingham Health Authority, the Cancer Research Campaign, and the Arthritis and Rheumatism Council for their financial support.

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Book review

Rheumatic Disease. By H.A. Capell, T.J. Daymond, W. Carson Dick. Pp. 196. £9.00. Springer-Verlag: Berlin. 1983.

This is the second monograph in a series aimed at filling a gap between standard textbooks, research reviews, and original articles in specialist fields. The first part consists of an introduction, followed by general principles and approach to a patient using osteoarthritis as a model. In the following 10 chapters due attention is paid to presentation with neck pain, pain in the low back, and the local syndromes of the shoulder, elbow, and carpal tunnel in the upper limbs, and tarsal tunnel, etc., in the lower limbs, as well as metabolic bone disease, crystal arthropathies, and arthritis associated with general medical disorders. Subsequent chapters included rheumatoid disease, juvenile chronic arthritis, the seronegative spondyloarthritides, infective arthritis, which somewhat strangely was continued with polymyalgia rheumatica and connective tissue disorders. There follow a further eight chapters, which start with the general principles of management of chronic arthritis, and then go through the pharmacology of the drugs used in the first and second line treatment, ending up with a chapter on surgery. There are few diagrams and no illustrations. The text is easy to read, and at the end of each chapter some general references for further reading are given.

This inexpensive paperback will be useful for people without particular knowledge who wish to learn rapidly something about rheumatology, whether they are at student, senior house officer, or registrar level. It should be especially useful for those general practitioners who want to take a more active role in looking after rheumatological patients in their own practice.

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