Lymphopenia in rheumatoid arthritis

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Summary

Lymphopenia is a recognized but poorly studied feature of rheumatoid arthritis (RA). We set out to establish the prevalence and significance of lymphopenia in RA. A group of 66 RA patients was studied for one year. During this time 10 (15%) had persistent lymphopenia (lymphocyte count less than 1.00×10^9/l) without evidence of Felty's syndrome. A separate study of lymphocyte subsets in 13 lymphopenic RA patients showed marked reduction in T-cell numbers with normal circulating B-cell numbers. The numbers of CD4 and CD8 positive T-cells were equally depressed. Lymphopenia may indicate more severe disease. It was not influenced by changes in disease activity or therapy.

Introduction

Lymphocytes play a central role in the pathogenesis of rheumatoid arthritis (RA). The rheumatoid synovium contains large numbers of lymphocytes and plasma cells[1], many of which bear the markers of activation[2]. Increased levels of circulating activated lymphocytes are also found in the peripheral blood[3-5]. In recent years much attention has been directed at identifying the different subsets of lymphocytes in RA peripheral blood. In these studies a number of groups have noted that some RA patients are lymphopenic[6-8]. However, no attempt has previously been made to establish the prevalence and significance of lymphopenia in RA. We describe two studies designed to address these questions.

Methods

Prevalence of lymphopenia (Longitudinal Study)

The study initially comprised 88 patients with definite or classical RA attending a therapeutic research clinic run by a single physician (MF) between 1 January and 31 December 1983. Each patient had a differential white cell count (WCC) performed at every clinic visit. During the year 66 patients (21 male, 45 female) had a differential WCC on two or more occasions (mean no. of counts 4.0 ± 1.6). Of these patients 13 were on non-steroidal anti-inflammatory drugs (NSAID) alone, 44 were on sulphasalazine, four were on d-penicillamine, one on gold and eight were taking corticosteroids. None of the patients was receiving cytotoxic drugs. Patients were said to be lymphopenic if they had at least two lymphocyte counts of 1.00×10^9/l or less during this year.

Lymphocyte subsets in lymphopenic RA patients

This study comprised 13 patients (3 male, 10 female) who were not included in the study above. They were attending a routine rheumatology outpatient clinic and were found to be lymphopenic from a routine blood count. All had definite or classical RA. None had leucopenia and none was taking a cytotoxic drug. Peripheral blood mononuclear cells (PBMC) were separated from heparinized blood by density centrifugation over Ficoll-Paque (Pharmacia). The PBMC were then washed three times and smeared onto Teflon and poly-l-lysine coated slides. The smears were stained with the monoclonal antibodies UCHT1 (Seward), OKT4, OKT8 (Ortho) and pooled anti-light chains to detect the CD3, CD4, CD8 and surface immunoglobulin positive cells respectively, using a method previously described[9]. The results were expressed in absolute numbers and compared with those of 41 controls using Student's *t*-test. The controls were healthy laboratory and departmental personnel.

Results

Prevalence of lymphopenia in RA

Thirteen (20%) of the 66 patients included in the longitudinal study had persistent lymphopenia. Two of these patients had Felty's syndrome and another became lymphopenic at the same time as she developed panhypogammaglobulinaemia (secondary to sulphasalazine). The other 10 (15%) patients had persistently low lymphocyte counts despite changes in disease activity and therapy. The lymphopenia was associated with leucopenia only in the two Felty's patients. All other patients had normal neutrophil and platelet counts.

Clinical data for the 10 patients whose lymphopenia could not be explained in terms of Felty's syndrome or a drug reaction are shown in Table 1 and details of treatment in Table 2. The mean age was 55.8 years (range 41-83) and mean disease duration 9.0 years

Table 1. Clinical and laboratory data in the longitudinal survey

	Lymphopenic (*n=10*)		*Non-lymphopenic* (*n=53*)		*P*
Male : female	1 : 1.5		1 : 2.5		
Seropositive	9(90%)		28(53%)		<0.05
	Mean	*Range*	*Mean*	*Range*	
Haemoglobin (g/dl)	12.2	(9.2-14.8)	12.8	(9.3-15.3)	NS
WCC ($\times10^9$/l)	6.3	(4.3-8.4)	7.7	(3.5-14.6)	<0.01
ESR (mm/1st hour)	30	(4-75)	37	(2-130)	NS
CRP (mg/l)	22	(4-62)	35	(4-168)	NS
Morning stiffness (min)	9	(0-15)	48	(0-360)	<0.01
Ritchie index	13	(3-32)	11	(0-20)	NS

These details exclude the two patients with Felty's syndrome and the one with drug-induced hypogammaglobulinaemia

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Table 2. Treatment details in the longitudinal survey

	Lymphopenic (n=10)		*Non-lymphopenic (n=53)*		
NSAID alone	3	(30%)	10	(19%)	NS
Sulphasalazine	5	(50%)	36	(68%)	NS
Penicillamine	1	(10%)	3	(6%)	NS
Gold	1	(10%)	0		NS
Steroids	0		8	(15%)	NS

Table 3. Lymphocyte subsets in 13 RA patients with lymphopenia (mean±SD)

	Lymphopenic RA patients (n=13)	*Healthy controls (n=14)*	*P*
Lymphocyte count	0.698±0.191	2.027±0.870	<0.001
CD3	0.478±0.163	1.448±0.613	<0.001
CD4	0.321±0.113	0.934±0.313	<0.001
CD8	0.152±0.051	0.509±0.231	<0.001
CD4 : CD8	2.14±0.42	1.93±0.48	NS
B	0.233±0.079	0.232±0.110	NS

NS, not significant

(range 1-25). The male to female ratio was greater in the lymphopenic patients and a significantly greater proportion were seropositive. The mean WCC was lower in the lymphopenic patients and they also had significantly less morning stiffness. There were no other significant differences in the indices of disease activity or in therapy between the two groups of patients.

Lymphocyte subsets in lymphopenic RA patients

The results of the lymphocyte subsets in the cross-sectional study of lymphopenic patients (Table 3) show that lymphopenia in RA is due to a decrease in the number of circulating T-cells. The numbers of CD4 and CD8 positive cells were equally depressed and the CD4 : CD8 ratio did not differ significantly from normal. The number of circulating B-cells in the lymphopenic RA patients was the same as in the controls.

Discussion

Lymphopenia is a recognized but poorly studied feature of RA. We have shown that 15% of our series of RA patients have persistent marked lymphopenia in the absence of Felty's syndrome or drugs known to reduce the lymphocyte count. The low lymphocyte count in these patients remained constant over long periods of time (extending beyond the duration of this study) and appeared to be uninfluenced by changes in drug therapy or disease activity. We have previously shown that, while sulphasalazine lowers the total WCC in RA, the lymphocyte count remains unchanged[10]. Isolated lymphopenia has not previously been attributed to d-penicillamine or NSAID therapy. A small study of 10 patients suggested that gold therapy reduced the absolute lymphocyte count[11] but a much larger study has since shown no change in the absolute lymphocyte count with either gold or penicillamine therapy[12].

We have shown that the lymphopenia in RA is due to a depression in circulating T-cell numbers while the number of circulating B-cells remains normal. The presence of this subset of RA patients with T lymphopenia may account for the widely varying results of lymphocyte subset analysis in this disease. If non-lymphopenic RA is associated with increased CD4 numbers and decreased CD8 numbers, the presence of a subset of lymphopenic patients with a normal CD4 : CD8 ratio could produce the following results in a random sample of RA patients: if there was a high proportion of lymphopenic patients the overall CD4 : CD8 ratio would be normal. If there were a moderate number of lymphopenic patients the CD4 numbers would be normal and the CD8 numbers reduced. If there were very few lymphopenic patients then the picture of increased CD4 and reduced CD8 numbers would emerge.

The clinical significance of lymphopenia in RA is not yet clear. Our results suggest that it is not simply a feature of disease activity. There were some suggestions that lymphopenia could be a marker of more severe disease (the higher prevalence of seropositivity).

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