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Rheumatoid factor in rheumatoid arthritis associated renal disease and in lupus nephritis

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SUMMARY To test the hypothesis that rheumatoid factor (RF) protects against (immune complex mediated) renal disease, patients with rheumatoid arthritis (RA; 48 with nephropathy of various types, 35 without renal disease) and systemic lupus erythematosus (SLE; 35 with and 17 without nephritis) were evaluated for the presence and titre of RF. There was no correlation between RF and nephropathy in RA, whereas in SLE RFs were almost exclusively seen in patients without nephropathy. This result supports the above hypothesis for lupus nephropathy but not for RA associated renal disease, and it may be explained by a more pronounced role for immune complexes in SLE and interference of RFs with the complexes.

Key words: rheumatic disease, systemic lupus erythematosus, glomerulonephritis.

Clinical observations have suggested that the presence of rheumatoid factor in patients with systemic lupus erythematosus is associated with mild forms or total absence of lupus nephropathy.[1 2] These observations, together with results from experimental in vitro[3–8] and in vivo[9 10] studies, have led to a hypothesis that RF protects from immune complex (IC) mediated renal disease (reviewed in Ref. 11). This hypothesis, also used to explain the relatively rare occurrence of glomerulonephritis (GN) in rheumatoid arthritis, has not been universally accepted. Series of SLE patients have been reported in which there is no such negative correlation between the presence of RF and lupus nephritis.[12 13] Further, a number of experimental works have shown that IgM RFs can aggravate nephritic manifestations[14] and augment the trapping of ICs in pre-existing glomerular immune deposits.[15 16]

Since the relationship between the presence or titre of RFs and the occurrence of renal disease in RA has not been systematically studied we compared RFs in RA patients with or without nephropathy. The renal diseases in RA patients included cases of amyloidosis, membranous glomerulonephritis, mild mesangial glomerulopathy, and some with clinical signs of renal disease and normal biopsy finding. To explore a possible correlation between RFs and glomerulonephritis in our patients with SLE we also studied two groups of lupus patients in a similar manner.

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Patients and methods

RA PATIENTS

The diagnosis of RA was based on the criteria of the American Rheumatism Association.[17] Forty eight RA patients with clinical signs of renal disease were subjected to percutaneous renal biopsy and represent part of the renal biopsy material of Tampere University Central Hospital from the years 1976 to 1985. The renal biopsy specimens were processed and examined as described previously.[18] Thirty three of the 48 RA patients had a 'classical', and 15 a 'definite' RA. A control group of 35 patients (without renal disease) consisted of 31 patients with classical, and four with definite disease. The control group was selected from consecutive patients of a rheumatology ward and patients with one or more of the following were excluded: daily urinary protein excretion >150 mg, haematuria of $>$four red blood cells per high power field, serum creatinine level >115 μmol/l.

SLE PATIENTS

The diagnosis of SLE was based on the 1982 revised

criteria of the ARA subcommittee for SLE criteria.[19] Out of the 35 lupus nephritis patients included in this study, 15 had four diagnostic criteria, 13 had five, six had six, and one patient had eight criteria. The above renal biopsy material included a representative renal biopsy specimen of 29 patients with lupus nephritis. The lesions in these specimens represented all classes of SLE glomerulonephritis:[20] four specimens had mesangial GN, six focal and 10 diffuse proliferative, and nine membranous GN. In a further six patients the diagnosis of lupus nephropathy was made on clinical grounds and confirmed by autopsy in one of them.

Seventeen SLE patients without nephritis were from the same nine year period, and they were randomly drawn from a computer listing. In this control group nine patients had four SLE diagnostic criteria, five had five, two patients had six, and one patient seven criteria. These patients were free of clinical signs of renal disease and they had no renal biopsy performed. Patients with signs of renal disease were excluded by the criteria described above for the RA patients.

ASSAY FOR RHEUMATOID FACTOR

RF was assayed by the sensitised sheep red blood cell agglutination (Waaler-Rose) test.[21] A titre of 1/64 was chosen for the lowest positive titre.

STATISTICAL EVALUATION

Testing of statistical significance of differences in RF titre between different groups of RA patients and controls was performed by the Kruskal-Wallis statistic. The significance of the correlation between renal disease and RF (SLE, RA) was tested by the χ^2 test.

Results

Our RA patients, biopsied for clinical signs of renal disease, had a variety of morphological lesions in the renal biopsy specimens. These and the biopsy indications are shown in Table 1. In RA patients the occurrence or titre of RF did not differ significantly between the nephropathy and control groups, nor between the different groups of renal disease (Table 2). Patients with mesangial glomerulopathy had some tendency towards higher RF titres, but the difference was not statistically significant. Nine out of the ten patients with membranous glomerulonephritis had received gold salts, and RF was positive in four. The renal patient and control RA groups were comparable with respect to such clinical

Table 1 *Renal biopsy indications and morphological findings in patients with rheumatoid arthritis*

Renal morphology	*Clinical renal finding (biopsy indication)*					
	HU	*PU*	*HU+PU*	*NS*	*CRF*	*Total*
Normal	2	1			1	4
Mesangial glomerulopathy	8	3	3	1*	1*	16
Membranous GN	2	5	2		1*	10
Amyloidosis		3	1	11	3	18
Total	12	12	6	12	6	48

HU=haematuria; PU=proteinuria; NS=nephrotic syndrome; CRF=chronic renal failure.
*Patients also had vascular amyloidosis.

Table 2 *Rheumatoid factor (RF) and renal disease in rheumatoid arthritis*

Reciprocal RF titre	*Patients with nephropathy (n=48), histological diagnosis*					*Patients without nephropathy (n=35)*
	Normal	*Amyl*	*Mes*	*MGN*	*Total*	
≤32	2	9	7	5	23	16
64–250	1	5	7**	5*	18	14
500–2000	1	4			5	5
≥4000			2		2	
Total	4	18	16	10	48	35
Percentage RF positive	50	50	56	50	52	54

Amyl=amyloidosis; Mes=mesangial glomerulopathy; MGN=membranous glomerulonephritis.
One patient with membranous GN (*) and two patients with mesangial glomerulopathy (**) also had vascular amyloidosis.

Table 3 *Rheumatoid factor (RF) and glomerulonephritis (GN) in systemic lupus erythematosus (No of patients)*

	GN		Total
	+	−	
RF positive	3	8	11
RF negative	32	9	41
Total	35	17	52
Percentage RF positive	9	47	21

parameters as age (52/23–73 *v* 53/30–73 years; median/range), disease duration (12/0–36 *v* 12/3–38 years), and stage of RA progression (Ref. 22; classes I+II/III+IV: 19/29 *v* 12/23 patients). The two groups did not match well in regard to the male to female ratio (21:27 in the renal patients *v* 7:28 in the control group).

In SLE patients there was a negative correlation between renal disease and the occurrence of RF (Table 3). The correlation was statistically significant ($p<0.005$). Only three patients with lupus nephropathy had positive RF at titres 1/64, 1/128, and 1/256. RF was positive in eight out of the 17 SLE patients who were clinically free of renal disease. The SLE patient populations were reasonably comparable: in the lupus nephritis group 3/35 patients were male *v* 1/17 in the control group; the age (median/range) of the patients was 34/12–67 *v* 46/18–73 years, and the disease duration 6/0·5–20 *v* 8/0·5–18 years.

Discussion

Our result from RF determinations in SLE patients is similar to that reported by Davis and Bollet,[1] who found an even more significant negative correlation between the occurrence of lupus nephropathy and RF. Another study speaking in favour of a protective role for RF in SLE is that by Hill *et al*,[2] in which RF was observed mainly in SLE patients with mild forms or no glomerulonephritis. In contrast, no correlation between RF and lupus nephropathy was found by Kantor *et al*[12] or Baldwin *et al*.[13] The reason for this discrepancy is unclear. One possibility is that the patient material or methods of investigation were different. In some of the works cited the patient data are not described in detail, which makes the comparison difficult. An example of possible differences of patient material or methods is the proportion of RF positive SLE patients in the above studies. This varied from 21% (the present work) to 53%.[13]

A negative correlation such as that in the SLE patients was not found between the presence or titre of RF and any of the renal disease groups in RA patients in our study. Nor was there any positive correlation between renal disease and RF. In this respect RA associated nephropathies seem to differ from such extra-articular RA manifestations as rheumatoid nodules, vasculitis, pulmonary fibrosis, lymphadenopathy, and splenomegaly, which are generally associated with high RF titres.[23]

In contrast with SLE, there are few data in the literature on the relation between RF and renal disease in RA. Skrifvars *et al* have suggested that the development of gold nephropathy may be related to an absence of IgM RF in serum.[24] In our patients RF negativity was not significantly associated with gold nephropathy: three out of eight patients with an obvious gold nephropathy had a positive RF titre. It is notable, however, that three of the five seronegative patients had earlier been seropositive (Waaler-Rose titres 1/250, 1/250, 1/500). Gold salts have been reported to reduce RF positivity,[25] which could result in loss of the protective effect. It is also possible that reduction of RF positivity and gold nephropathy are not causally related but rather two independent sequels of gold therapy. An association has recently been reported between systemic amyloidosis and seronegativity in adult rheumatoid arthritis.[26] In that study RFs were determined by an enzyme immunoassay and the results may not be comparable with ours obtained by a different technique. Half of our patients with amyloidosis had RF titres higher than 1/64.

In our patients RFs were almost exclusively observed in lupus patients without nephropathy, whereas in RA RF positivity was equally common in patients with and without renal disease. This result is compatible with RFs exerting a protective effect against renal disease in SLE but not in RA. This could be explained by different mechanisms producing tissue lesions in these two disorders. The glomerular injury in SLE is regarded as a prototype immune complex lesion.[27] RFs could interfere with ICs or the sequels of IC formation, e.g., complement activation, or facilitate elimination of ICs. Such effects of RFs have been shown in numerous in vitro and also in vivo models.[3 11] The pathogenesis of RA associated renal disease is less well delineated and without doubt heterogenous, and it is possible that ICs in these disorders have a less central role. Even though ICs would be pathogenetically significant as in gold induced membranous glomerulonephritis,[28] other IC related factors, e.g, complement activation, could be different between the renal disease in SLE and RA.

In our opinion the relatively rare occurrence of

nephropathies in RA can hardly be explained by RFs. In this connection, reference is often made to SLE, which is regarded as pathogenetically similar,[29] and in which there are renal manifestations in at least 70% of patients.[30] We think that a feasible explanation for the different prevalence of kidney disease in RA and SLE is the presence of factors which favour the production of renal glomerular injury in SLE. Immunopathological features, typical of SLE, that make the kidney tissue one of the major targets of immunological injury in SLE include among others abundant circulating ICs of varying composition, a strong complement activating potential of DNA ICs,[27] and a high affinity of DNA to bind to the glomerular basement membrane.[31]

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