Determination of IgA- and IgM-rheumatoid factors in patients with rheumatoid arthritis with and without nephropathy

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Abstract

***Objective*—To clarify the characteristics and pathogenesis of renal disorders in patients with rheumatoid arthritis (RA).**

***Methods*—In this study, 143 patients with RA were included, from whom 43 with urinary abnormalities were biopsied. Serum rheumatoid factor (RF) concentrations of IgA and IgM isotypes were also measured in these patients by enzyme linked immunosorbent assay.**

***Results*—Light microscopy of renal biopsy specimens showed minor glomerular abnormalities in six patients, mesangial proliferative glomerulonephritis (GN) in 21, membranous nephropathy in seven, renal amyloidosis in seven, and tubulointerstitial nephritis in two. Twelve patients with mesangial proliferative GN and one with minor glomerular abnormalities were found by immunofluorescence microscopy to have abnormalities consistent with IgA GN. Although the concentrations of IgA-RF in patients with IgA GN were slightly raised compared with those with glomerulopathy established by biopsy but not associated with IgA GN, the concentrations of IgA-RF were higher in patients with RA with vasculitis or interstitial pneumonia than those with RA complicated by IgA GN.**

***Conclusions*—Mesangial proliferative GN, including IgA GN, may be a frequent renal lesion in Japanese patients with RA. IgA-RF may play little pathogenetic part in the development of IgA GN in RA.**

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Renal amyloidosis[1-3] and membranous nephropathy (MN) secondary to treatment with gold or D-penicillamine[3-8] have been described as major complications of rheumatoid arthritis (RA). Some renal problems have also been associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), including interstitial nephritis, papillary necrosis, and nephrotic syndrome.[9-13]

Although glomerulonephritis (GN) had been thought to be rare in patients with RA,[14] mesangial proliferative lesions have been recognised to be the most dominant glomerular abnormality as determined by light, electron, and immunofluorescence microscopy in recent studies.[3 15-17] Accumulated clinical data from several studies have disclosed that the occurrence of isolated mesangiopathy in patients with RA is not associated with drug treatment.[3 15 18]

On the other hand, it has been postulated that rheumatoid factor (RF) may play some pathogenetic part in the development of some types of GN.[19-22] More recently, immunological comparison of patients with RA with various forms of nephropathy with those without clinical renal disease showed no difference in RF and immune complex determinations.[23]

We studied the renal lesions of 43 patients with RA and urinary abnormalities by light, electron, and immunofluorescence microscopy. Concentrations of IgA and IgM isotype RF were also measured in serum samples from these patients to investigate the relation between class specific RFs and renal lesions such as IgA GN.

Patients and methods

PATIENTS

Patients admitted to our clinic from 1979 to 1995 were included in the study. There were 143 patients, 38 men and 105 women, mean age at admission 55·4 (SD 12·6) years (range 20–84). The mean duration of RA before admission was 10·3 (8·7) years (range 6 months–53 years). All patients satisfied the 1987 revised criteria of the American College of Rheumatology for RA.[24] Patients with RA who also had systemic lupus erythematosus, mixed connective tissue disease, or progressive systemic sclerosis were excluded from the study.

The radiological progression of RA was determined as advocated by Steinbrocker *et al.*[25] The antirheumatic drugs used before the renal biopsy were surveyed retrospectively from the hospital charts. Intravenous urograms were performed in all biopsied patients and no serious urological abnormalities were detected. Urinary tract infection was ruled out by culture of midstream urine.

RENAL BIOPSY

Renal biopsy was performed because of clinical or laboratory evidence of renal disease, after obtaining each patient's informed consent. Histological evaluations were performed by light, electron, and immunofluorescence microscopy. Light microscopic evaluation was

done after staining with haematoxylin and eosin, periodic acid Schiff, periodic acid methonamine silver (PAM), PAM Masson, elastica Masson, and Congo red. Immunofluorescence studies were performed on cryostat sections using fluorescein isothiocyanate conjugated antisera to human immunoglobulins (IgG IgA, and IgM), complement (C3, C4, and C1q), and fibrinogen. In patients with renal amyloidosis, the potassium permanganate reaction was used to distinguish between primary and secondary amyloidosis. The presence of characteristic non-branching fibrils on electron microscopy confirmed the diagnosis of renal amyloidosis.

RENAL FUNCTION AND URINARY EXAMINATION

Renal function at the time of admission was determined from serum creatinine measurements. Loss of renal function was assumed when the serum creatinine exceeded 1·2 mg/dl. Haematuria was defined as ≥five red blood cells per high power field on urinalysis. Proteinuria was defined as urinary protein excretion ≥0·3 g/24 h and nephrotic range proteinuria ≥3·5 g/24 h.

IMMUNOLOGICAL DETERMINATIONS

Serum immunoglobulins (IgG, IgA, and IgM) and serum complement factors (C3 and C4) were measured by laser nephelometry. Conventional RF activity was determined by turbidity immunoassay (TIA-RF). TIA-RF activity was defined as abnormal when the serum concentration exceeded 10 IU/ml.

MEASUREMENT OF CLASS SPECIFIC RFs

IgA-RF and IgM-RF were detected by enzyme linked immunosorbent assays (ELISA) as described by Bampton *et al*[26] with minor modifications. Briefly, rabbit IgG (R-IgG) was used as antigen and R-IgG (50 µl) at a concentration of 10 µg/ml in 50 mM sodium carbonate buffer pH 9·6 was added to Nunc ELISA microtitre plates. Wells containing only sodium carbonate buffer (50 µl) were prepared as controls. The plates were incubated overnight at 37°C, then washed three times with Tris-HCl buffer (0·15 M Tris, pH 7·6) containing 0·05% Tween 20 and 0·2% gelatin (washing solution).

After IgG coating, bovine serum albumin (20 mg/ml) in washing solution was treated for two hours at room temperature to block non-specific antibody adsorption. After washing three times, serum diluted 1:200 in washing solution was added to each well. The plates were incubated for six hours at 4°C and then washed three times. The peroxidase conjugated second antibody diluted 1:2000 in washing solution was added to each well and the plate incubated at 4°C for two hours. After washing three times with washing solution, 100 µl of substrate solution (*o*-phenylenediamine) was added. The solution was then incubated for 20 minutes, followed by addition of 100 µl 1 N H_2SO_4. IgA-RF and IgM-RF were measured in 61 patients and 27 normal controls.

The optical density was measured and the results were compared with the density of normal pooled sera as described by Powell *et al*[27] or Gioud-Paquet *et al*.[28] The results were expressed as:

(mean OD with Ag – mean OD without Ag) test serum/(mean OD with Ag – mean OD without Ag) normal pooled sera

where OD = optical density; Ag = antigen.

Mean (SD) serum IgA-RF and IgM-RF concentrations in 27 normal controls were 1·06 (0·62) and 1·08 (0·51), respectively. The upper limits of the normal range for IgA-RF and IgM-RF were defined by the mean + 2SD of the normal controls as 2·3 and 2·1 respectively. The same normal pooled sera were used for all assays.

Serum samples were stored at –70°C before use.

STATISTICS

Statistical analysis by Student's *t* test and χ^2 test was used to assess subgroup differences in age at renal biopsy, duration of RA, stage of RA, immunoglobulins, class specific RFs and TIA-RF, urinalysis findings, and serum creatinine.

Results

Renal biopsy was performed in 43 out of 143 patients. Table 1 shows the biopsy findings. The common nephropathy types included mesangial proliferative glomerulopathy in 21 patients, MN, and secondary amyloidosis in seven. Twelve of 21 patients with mesangial proliferative GN and one with minor glomerular abnormalities were classified as IgA GN, because the main glomerular immunofluorescence finding in the biopsy specimen was diffuse global IgA deposition.[29] There was no significant difference between patients with mesangial proliferative GN and other renal histopathology groups for sex or the use of antirheumatic drugs; non-steroidal anti-inflammatory drugs (NSAIDs) had been used in every patient. Three of seven patients with RA with MN received no antirheumatic drug at any point.

Non-renal extra-articular manifestations, including vasculitis and interstitial pneumonia, were recognised in 23 patients. The histological diagnosis of secondary amyloidosis was made from biopsies of the rectum, upper

Table 1 Renal histological classification by light microscopy

Classification	*Patients (n)*	*Sex M/F*	*Drug history*	
			Gold	*D-PC*
Minor glomerular abnormality	6	0/6	6	2
Mesangial proliferative GN	21	5/16	19	4
Amyloidosis	7	0/7	5	4
Membranous nephropathy	7	3/4	4	2
Tubulointerstitial nephritis	2	0/2	1	0
No histological evaluation	100	30/70	—	—

D-PC = D-penicillamine.
Values are numbers of patients.

gastrointestinal tract, or abdominal wall fat in 19 other patients who underwent no renal histological evaluation. Renal disorders were recognised without histological examination in 12 other patients.

According to clinical and histological findings, the patients were divided into six subgroups: (*a*) patients with IgA GN (IgA GN; n = 13); (*b*) patients with minor glomerular abnormalities and mesangial glomerulopathy except for IgA GN (non-IgA GN; n = 14); (*c*) patients with secondary amyloidosis (amyloidosis; n = 26); (*d*) patients with vasculitis or interstitial pneumonia (vasculitis; n = 23); (*e*) patients with MN (membranous) (n = 7); (*f*) patients without clinical renal manifestations (controls; n = 46). Patients with interstitial nephritis (n = 2) and patients with renal disorder who underwent no histological evaluation (n = 12) were excluded from this study.

The vasculitis group and amyloidosis group were significantly older than the group with IgA GN but were not significantly different from the controls. The mean duration of RA, however, was significantly longer in the amyloidosis group than in the group with vasculitis, the membranous group, or controls. Further, the mean stage of RA was significantly more advanced in patients with amyloidosis than in any other group (table 2).

Proteinuria was commonly found in patients with amyloidosis (21/26; 81%) and the membranous group (6/7; 86%), but the incidence of proteinuria was relatively low in patients with IgA GN (5/13; 38%) or non-IgA GN (3/14; 21%). Nephrotic syndrome was recognised more often in patients with membranous (4/7; 57%) and amyloidosis (7/26; 27%). Definite haematuria was, however, often seen in patients with IgA GN (13/13; 100%) or non-IgA GN (12/14; 86%), therefore isolated haematuria was prevalent in patients with RA and mesangiopathy. The incidence of haematuria in patients with amyloidosis was 50% (13/26). Renal dysfunction was often seen (19/26; 73%) in patients with amyloidosis; however, renal dysfunction was infrequent in patients of other groups (table 3).

Table 4 shows serum immunoglobulin concentrations. Mean serum IgG and IgA concentrations were significantly higher in the vasculitis group than in the group with amyloidosis. The concentrations of IgG were also higher in the vasculitis group than in the non-IgA GN group. Mean serum IgA concentrations in patients with IgA GN were comparable with those in other groups.

Table 5 shows the results of comparative studies of class specific and conventional RFs. Mean IgA-RF and IgM-RF concentrations were significantly higher in the vasculitis group than in any other group. The concentrations of TIA-RF were also significantly higher in the vasculitis group than in any other group except for the group with IgA GN. Also, mean IgA-RF concentrations were slightly higher in patients with IgA GN than in the non-IgA GN group.

Table 2 Comparison of age, duration of disease and stage of RA

Group (n)	*Age (y)*	*Duration (y)*	*Stage of RA*
IgA GN (13)	46·2 (9·3)**[1] **[2]	11·3 (6·5)	2·7 (1·3)**[2]
Non-IgA GN (14)	53·8 (13·9)	10·2 (9·2)	2·3 (1·0)*[2]
Amyloidosis (26)	60·0 (10·2)	16·3 (11·5)	3·8 (0·4)
Vasculitis (23)	59·2 (7·9)	8·4 (8·1)**[2]	2·6 (0·8)**[2]
Membranous (7)	52·3 (12·8)	8·0 (5·4)*[2]	2·7 (1·1)*[2]
Control (46)	54·7 (15·0)	8·0 (6·9)**[2]	2·4 (1·1)**[2]

Values are mean (SD).
*p < 0·05, **p < 0·01; 1 = *v* vasculitis; 2 = *v* amyloidosis.

Table 3 Renal presentation in various groups of patients with RA

Group (n)	*Proteinuria ≧0·3 g/day*	*Nephrotic syndrome*	*Haematuria ≧5 RBC/hpf*	*Serum Cr >1·2 mg/dl*
IgA GN (13)	5	0	13	1
Non-IgA GN (14)	3	1	12	0
Amyloidosis (26)	21	7	13	19
Vasculitis (23)	0	0	3	0
Membranous (7)	6	4	1	2
Control (46)	0	0	0	0

Values are numbers of patients.
RBC = red blood cells; hpf = high power field; Cr = creatinine.

Table 4 Comparison of the concentrations of immunoglobulin G, A, and M

Group (n)	*IgG (mg/dl)*	*IgA (mg/dl)*	*IgM (mg/dl)*
IgA GN (13)	1508 (619)	395 (107)	160 (88)
Non-IgA GN (14)	1536 (470)*	398 (223)	218 (199)
Amyloidosis (25)	1491 (694)*	349 (173)*	223 (227)
Vasculitis (20)	2016 (842)	505 (285)	208 (96)
Membranous (7)	1218 (666)	400 (196)	157 (22)
Control (41)	1870 (622)	399 (188)	167 (82)

Values are mean (SD).
*P < 0·05 *v* vasculitis.

Table 5 Comparison of class specific and conventional rheumatoid factors

Group	*IgA-RF (n)*	*IgM-RF (n)*	*TIA-RF (n)*
IgA GN	8·6 (9·2, 11)*[1]	8·0 (9·4, 11)*[1]	340 (589, 8)
Non-IgA GN	2·3 (1·8, 6)**[1] *[2]	2·7 (2·3, 6)**[1]	60 (39, 9)**[1]
Amyloidosis	7·1 (6·6, 10)*[1]	7·5 (7·8, 10)*[1]	194 (301, 21)*[1]
Vasculitis	16·6 (11·1, 17)	18·6 (13·9, 17)	775 (830, 17)
Membranous	4·6 (3·7, 4)*[1]	4·6 (6·1, 4)*[1]	66 (73, 6)**[1]
Control	5·1 (4·0, 17)**[1]	5·6 (4·8, 17)**[1]	115 (159, 34)**[1]

Values are mean (SD).
*p < 0·05, **p < 0·01; 1 = *v* vasculitis, 2 = *v* IgA GN.

Discussion

Renal failure has been thought to be one common cause of death in patients with RA, and histologically renal amyloidosis has been perceived as a main cause of renal failure in several studies.[30 31] Prolonged inflammation accompanied by chronic polyarthritis has been considered to be responsible for the occurrence and progression of secondary amyloidosis in patients with RA.[32 33] The present study confirmed the concept that patients with longstanding and advanced RA may be prone to secondary amyloidosis, and that secondary amyloidosis may be the major cause of renal failure in these patients, whereas the low IgG concentrations in this group were considered to be connected to the high frequency of profuse proteinuria.

Membranous nephropathy has also been described as a major complication in patients with RA, usually associated with the use of antirheumatic drugs such as gold or D-penacillamine.[5 6 8] In our study, antirheumatic drugs were recognised as re-

sponsible for the occurrence of MN in four out of seven patients, although three other patients received no antirheumatic drug when their renal disorder developed. There have been several cases of MN in patients with RA not treated with antirheumatic drugs.[34] Further, Samuels *et al*[35] assumed that the nephropathy may be linked pathogenetically to the RA. Further studies are needed to resolve these problems.

Glomerulonephritis had been considered, until about 20 years ago, to be a rare complication of RA.[14 36 37] In recent renal biopsy electron and immunofluorescence microscopy studies, mild mesangial proliferative GN has been shown to be a common finding in patients with RA presenting with haematuria or proteinuria.[3 15-18] Our study of renal biopsy specimens by light microscopy showed also that an increase in mesangial matrix or mesangial cells was a common histological abnormality in patients with RA, and that most of these patients presented with haematuria dominant urinary abnormalities. There is little evidence regarding NSAID induced mesangial glomerulopathy,[9 10] and a relation between exposure to antirheumatic drugs and haematuria has not been well established.[18 38-41] Therefore, it is plausible that these urinary findings are associated with mesangial glomerulopathy itself.[3]

Recent immunopathological analyses of renal disorders in patients with RA have yielded somewhat conflicting results. For example, Korpela *et al*[18] found that the most common immunofluorescence finding in mesangial GN associated with RA was mesangial IgM deposition, even though in many cases of mesangiopathy, no deposition was seen.[4 42] More recently, patients with RA complicated by IgA GN have been reported sporadically,[23 43 44] and IgA GN was often found in our study of Japanese patients with RA.

Systemic rheumatoid vasculitis with extra-articular lesions has been related to high titres of RF in several studies.[45 46] A similar positive correlation between RFs and extra-articular features was noted in the present study. Moreover, RFs have been assumed to have a pathogenetic role in the development of some types of GN,[21 22 47-50] whereas, Korpela *et al*[23] reported that RFs may not have any role in the pathogenesis of various nephropathies in patients with RA. Also, protective roles for RF have been suggested by several studies.[51-53] To clarify the pathogenesis of IgA GN in patients with RA, we examined class specific RFs, including IgA-RF. There was little correlation between histopathological injury to kidney tissue and the serum concentration of any class of RF, although the mean IgA-RF concentration was slightly higher in patients wth IgA GN than in the group with non-IgA GN.

Certain genetic or geographic factors have also been related to the onset of primary IgA GN. Fauchet *et al*[54] found a significant association of HLA-DR4 with primary IgA GN (48·8% in 45 patients with IgA GN versus 19·5% in the controls). A similar finding in Japanese patients was reported by Hiki *et al*.[55] HLA-DR4 antigen is also thought to be related to the occurrence and progression of RA in several countries.[56 57] Therefore, a common pathogenetic basis may exist that explains the concurrence of RA and IgA GN. However, because IgA GN is the most common primary glomerular disease in the Japanese population,[55 58] the prevalence of IgA GN in Japanese patients with RA in our study may be related to the high frequency of IgA GN in the Japanese population. This may explain why Korpela *et al*[23] reported that the frequency of IgA GN in patients with RA was nearly equal to that seen in the general population.

In the present study, renal function was maintained in every patient with mesangiopathy except for one patient with IgA GN. Although primary IgA GN was thought to take a benign course, some cases did progress to end stage renal failure after 10 to 20 years.[59] From their longitudinal study of patients with RA, Korpela *et al* also showed that one out of three cases with IgA GN developed end stage renal failure.[18] Therefore, the clinical course of IgA GN in patients with RA may be similar to that of primary IgA GN.

In conclusion, renal histological evaluation showed that mesangial proliferative GN with mesangial IgA deposits was the most common type of nephropathy in Japanese patients with RA. Little correlation was found between mesangial glomerulopathy and the serum concentration of any class of RF. Further study should aim to clarify the role of IgA RF in the development of IgA GN in patients with RA. Although renal dysfunction was infrequent in our patients with RA and mesangial glomerulopathy, careful prospective studies may be necessary for such patients because the natural course and importance of the disease combination are not fully understood.

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