Mod Rheumatol (2002) 12:148–154

ORIGINAL ARTICLE

Hirofumi Makino · Yasuhiko Yoshinaga
Yasushi Yamasaki · Yoshitaka Morita · Hiroo Hashimoto
Masahiro Yamamura

Renal involvement in rheumatoid arthritis: analysis of renal biopsy specimens from 100 patients

Received: May 14, 2001 / Accepted: November 17, 2001

Abstract We analyzed renal biopsy specimens from 100 patients to evaluate the characteristics of renal involvement in patients with rheumatoid arthritis (RA). Membranous nephropathy (MN) was the most common renal histological pattern (31%). Mesangial proliferative glomerulonephritis (GN) was found in 21% of cases (IgA nephropathy 12%, non-IgA GN 9%), minor changes in 17%, renal amyloidosis in 11%, interstitial nephritis in 9%, sclerotic GN in 4%, and crescentic GN in 2%. MN was relatively more frequent in men than in women, and most developed nephrotic syndrome, while a few developed renal failure. Disease-modifying antirheumatic drugs (DMARDs) correlated with MN in 26 of 31 cases. Mesangial proliferative GN showed high-grade hematuria. Amyloidosis correlated with long duration of RA; approximately half of the cases with amyloidosis also had nephrotic syndrome, and 82% developed renal failure. Of the 100 patients, 82% showed some tubulointerstitial changes, which might be related to non-steroidal anti-inflammatory drugs. Because renal lesions in RA are very diverse, and early stage cases of MN and amyloidosis can be detected only by histological examinations, renal biopsy should be performed in cases with continuous urinary abnormalities or progressive renal failure.

Key words Disease-modifying antirheumatic drugs (DMARDs) · Glomerulonephritis (GN) · Renal biopsy · Rheumatoid arthritis (RA)

H. Makino (✉) · Y. Yamasaki · Y. Morita · M. Yamamura
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine and Dentistry, 2-5-1 Shikata-cho, Okayama 700-8558, Japan
Tel. +81-86-235-7232; Fax +81-86-222-5214
e-mail: makino@med.okayama-u.ac.jp

Y. Yoshinaga
Department of Rheumatology, National Minami-Okayama Hospital, Okayama, Japan

H. Hashimoto
Department of Medicine, National Hospital Okayama Medical Center, Okayama, Japan

Introduction

Rheumatoid arthritis (RA) is the most common collagen disease, the prevalence of which has been reported to be 0.3%–1.5%.[1] This is approximately 20 times that of systemic lupus erythematosus (SLE). In SLE, the kidney is the most important target organ; lupus nephritis is a complication in approximately two-thirds of SLE cases. No inherent renal lesions are known in RA,[2] but urinary abnormalities and renal dysfunction are common. In a previous study of 154 outpatients with RA, we reported that urinary abnormalities such as proteinuria and hematuria were found in one-third of the cases, and urinary levels of beta 2-microglobulin (BMG) and N-acetyl-beta-D-glucosaminidase (NAG), the indicators of tubular damage, were high in 18.4% and 50% of cases, respectively.[3]

Renal dysfunction is occasionally intractable, and some patients develop chronic renal failure and require dialysis. Renal failure is one of the important prognostic indicators in patients with RA.[4] The incidence of renal insufficiency, including amyloidosis, has recently increased markedly in Japan.[5] The urinary abnormalities and renal dysfunction in RA are thought to be induced by disease-modifying antirheumatic drugs (DMARDs),[6,7] nonsteroidal anti-inflammatory drugs (NSAIDs),[8] and secondary amyloidosis.[9]

As published, detailed studies based on large numbers of renal biopsy specimens are limited,[10,11] renal involvement in 100 patients with RA was analyzed histologically in this study.

Patients and methods

We studied renal histopathological findings from 100 renal biopsy specimens, 20 men and 80 women, with a mean age of 53.1 ± 13.6 years (mean ± SD, range 17–78 years), and a mean RA duration of 9.9 ± 8.9 years. All the patients fulfilled the American Rheumatism Association 1987 re-

vised criteria for the classification of RA. The numbers of patients in Steinbrocker stages I, II, III, and IV were 23, 23, 21, and 33, respectively, and the numbers of patients in Steinbrocker (activities of daily living) classes 1, 2, 3, and 4 were 39, 37, 21, and 3, respectively. The numbers of patients who were receiving gold sodium thiomalate, D-penicillamine, bucillamine, lobenzarit disodium, methotrexate, sulfasalazine, auranofine, mizoribine, and actarit when the urinary abnormality appeared were 27, 17, 27, 3, 2, 2, 1, 1, and 1, respectively. No patient was prescribed more than two kinds of DMARDs simultaneously, and nine patients had never received any DMARDs. Renal biopsies were performed at Okayama University Hospital from 1977 to 1999, with informed consent, because of urinary abnormalities and/or renal dysfunction.

Proteinuria was defined as more than 0.5 g in urine samples collected in 1 day, and hematuria was defined as urine sedimentary red blood cell counts of more than five in the visual field of a ×400 microscope. The grades of hematuria were expressed as follows: grade 1, ≥5; grade 2, 6–20; grade 3, 21–50; grade 4, >50. Renal function was evaluated by serum creatinine (Cr) and creatinine clearance (Ccr). Renal failure was defined as Cr ≥1.5 mg/dl or Ccr ≤40 ml/min.

Renal histopathology was evaluated by light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). At least ten glomeruli were observed in each specimen with LM. The LM evaluation was performed after staining with hematoxylin and eosin (HE), periodic acid Schiff (PAS), periodic acid methenamine silver (PAM), elastica Masson, and Congo-red or Dylon. The IF study was performed on cryostat sections using fluorescein isothiocyanate conjugated antisera to human immunoglobulins (IgG, IgA, IgM), complements (C1q, C3), and fibrinogen. EM was performed using standard procedures.

We studied the relationship between renal histology and clinical parameters such as urinalysis, renal function, age, gender, duration, and RA stage.

Student's *t*-test was used for the statistical analysis. Differences between mean values with *P* values of less than 0.05 were considered to be significant. StatView J-Ver.5.0 (Abacus Concepts) was used for the statistical analysis.

Results

Renal histology in RA

Membranous nephropathy (31%) was the most common of the renal histological patterns found in the 100 cases; mesangial proliferative glomerulonephritis (GN) was found in 21% (IgA nephropathy, 12%; non-IgA GN, 9%), minor changes in 17%, renal amyloidosis in 11%, interstitial nephritis in 9%, sclerotic GN in 4%, and crescentic GN in 2%. The remaining 5% were complications of SLE (4%) and type 2 diabetes mellitus (1%).

The relation between urinalysis and renal histology is shown in Fig. 1. The 100 cases were divided into four groups according to the urinalysis results: proteinuria and hematuria (50%), proteinuria only (34%), hematuria only (11%), and no urinary abnormality (5%). Membranous nephropathy appeared in the majority of the proteinuria and hematuria group, and in the proteinuria only group. Mesangial proliferative GN (IgA nephropathy and non-IgA GN) was frequent in the hematuria only group, as well as in the proteinuria and hematuria group. Amyloidosis was seen in the proteinuria only group, as well as in the proteinuria and hematuria group.

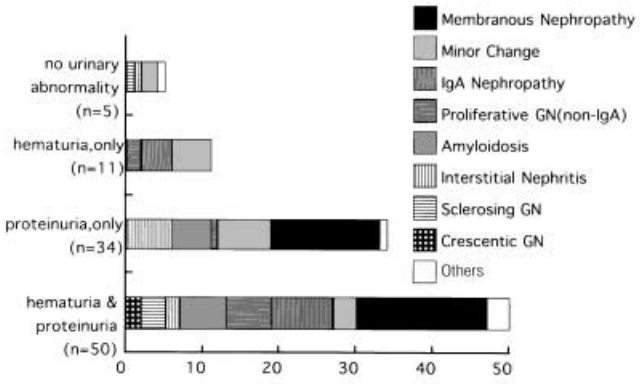

Fig. 1. Relation between urinalysis and renal histology. The 100 cases were divided into four groups according to the urinalysis results: proteinuria and hematuria, proteinuria only, hematuria only, and no urinary abnormality. Membranous nephropathy appeared in the majority of the cases in the proteinuria and hematuria group, and in the proteinuria only group. Mesangial proliferative glomerulonephritis (*GN*) (IgA nephropathy and non-IgA GN) was frequent in the hematuria only group, and in the proteinuria and hematuria group. Amyloidosis was seen in the proteinuria only group, and in the proteinuria and hematuria group

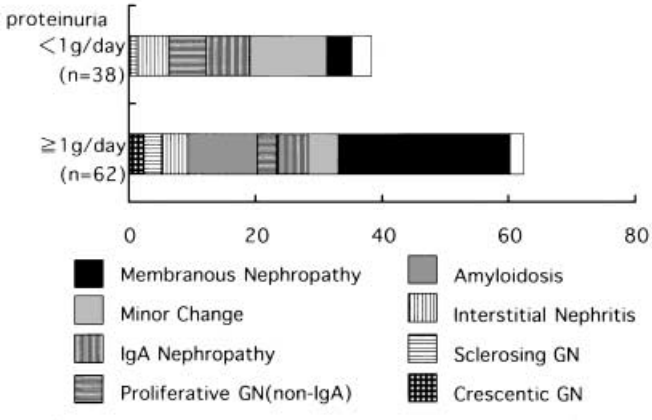

Fig. 2. Relation between proteinuria and renal histology. Proteinuria of more than 1 g/day was found in 62% of cases. In these cases, membranous nephropathy was the most common histological pattern, followed by amyloidosis

The relation between proteinuria and renal histology is shown in Fig. 2. Proteinuria of more than 1 g/day was found in 62% of cases. In these cases, membranous nephropathy was the most common histological pattern, followed by amyloidosis.

The relation between renal function and renal histology is shown in Fig. 3. In renal failure (serum creatinine ≥1.5 mg/dl), amyloidosis was the most common histological

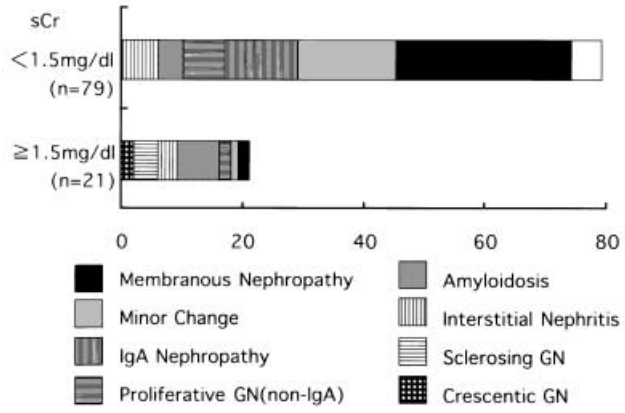

Fig. 3. Relation between renal function and renal histology. Renal failure (serum creatinine ≥1.5 mg/dl) occurred in 21% of cases. In these cases, amyloidosis was the most common histological pattern, followed by sclerosing GN, interstitial nephritis, and crescentic GN, in descending order. Membranous nephropathy and mesangial proliferative GN each appeared in over one-third of cases in the normal renal function (serum creatinine <1.5 mg/dl) group, but each appeared in less than 10% of cases in the renal failure group

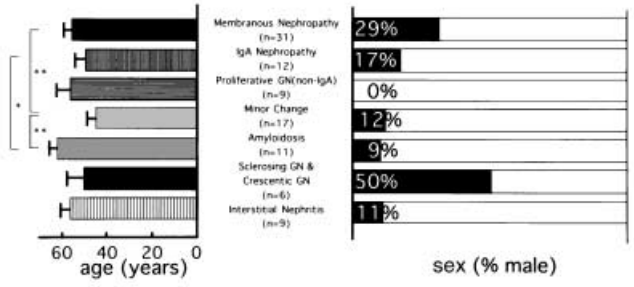

Fig. 4. Relation between age, sex, and renal histology. Minor changes and IgA nephropathy were found in younger patients, and amyloidosis, membranous nephropathy, and interstitial nephritis were found in older patients. Sclerosing GN/crescentic GN and membranous nephropathy were relatively more frequent in men than in women. $*P < 0.05$; $**P < 0.01$

pattern, followed by sclerosing GN, interstitial nephritis, and crescentic GN, in descending order. Membranous nephropathy and mesangial proliferative GN each appeared in more than one-third of the normal renal function (serum creatinine <1.5 mg/dl) group, but each appeared in less than 10% of the renal failure group.

Characteristics of each renal histological pattern

Minor change and IgA nephropathy were found in younger patients, and amyloidosis, membranous nephropathy, and interstitial nephritis were found in older patients (Fig. 4). Sclerosing GN/crescentic GN and membranous nephropathy were relatively more frequent in men than in women. Amyloidosis and interstitial nephritis were seen in patients with long duration and advanced stages of RA (Fig. 5). Proteinuria was massive in cases of membranous nephropathy and amyloidosis. The grade of hematuria was high in mesangial proliferative GN, including IgA nephropathy (Fig. 6). Renal function estimated by Cr or Ccr was significantly decreased in sclerosing GN/crescentic GN, and in amyloidosis (Fig. 7).

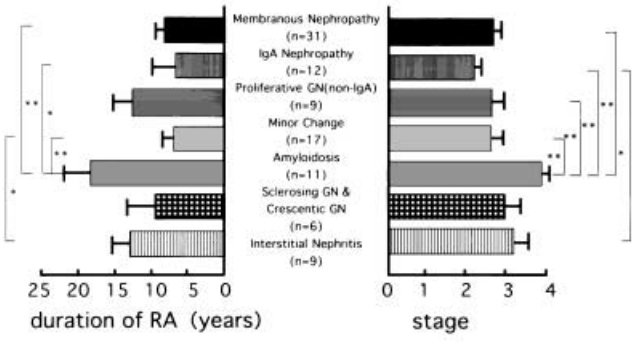

Fig. 5. Relation between duration, stage of RA, and renal histology. Amyloidosis and interstitial nephritis were seen in patients with long-duration and advanced stages of RA. $*P < 0.05$; $**P < 0.01$

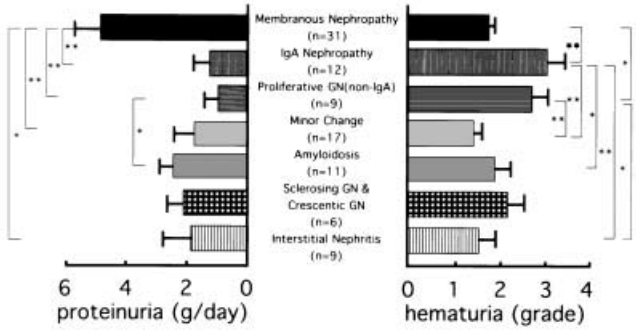

Fig. 6. Relation between urinalysis and renal histology. Proteinuria was massive in membranous nephropathy. The grade of hematuria was high in mesangial proliferative GN, including IgA nephropathy. The grades of hematuria were expressed as follows: grade 1, ≤5; grade 2, 6–20; grade 3, 21–50; grade 4, >50. $*P < 0.05$; $**P < 0.01$

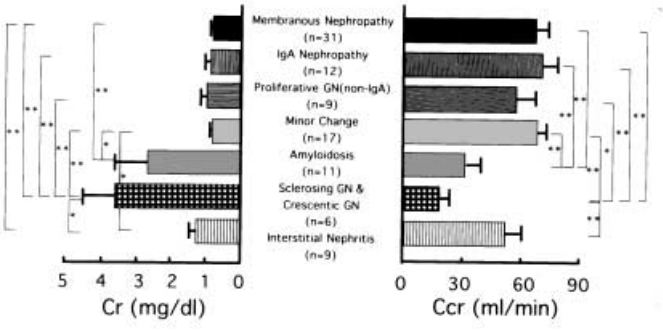

Fig. 7. Relation between renal function and renal histology. Renal function, estimated by Cr or Ccr, was significantly decreased in sclerosing GN/crescentic GN and in amyloidosis. $*P < 0.05$; $**P < 0.01$

Membranous nephropathy in RA

Membranous nephropathy was the most common nephropathy in the 100 cases (31%, 10 men and 21 women), and occurred in men in a relatively higher ratio by sex (see Fig. 4). The 31 cases showed massive proteinuria (4.9 ±

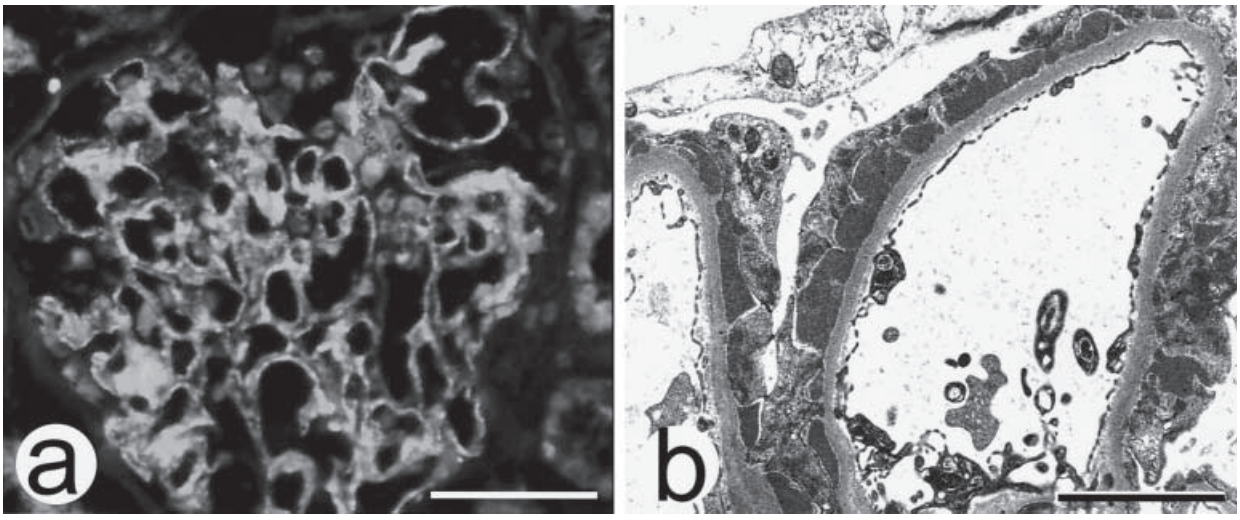

Fig. 8. Renal biopsy findings of membranous nephropathy in RA. **a** Immunofluorescence technique. The deposition of immunoglobulin G and complements along the capillary wall can be seen. *Bar* 50 μm. **b** Electron microscopy. Subepithelial electron-dense depositions can be seen, but most of the cases were graded as early stage (stages I and II) by Ehrenreich and Churg's classification. *Bar* 5 μm

Table 1. Causal DMARDs of membranous nephropathy in RA

Causal DMARDs	Number of cases
D-penicillamine	6
Gold sodium thiomalate	5
Bucillamine	13
Actarit	1
Unknown	5
Other[a]	1

DMARD, disease-modifying antirheumatic drug
[a] Uterine cancer was revealed by further examination

4.0 g/day), and most of them presented nephrotic syndrome ($n = 19$) but less hematuria (grade 1.8 ± 0.8). Renal function was maintained in the normal range (Cr 0.9 ± 0.3 mg/dl, Ccr 69.4 ± 28.1 ml/min). Based on the clinical evaluation of each case of membranous nephropathy, the DMARDs, bucillamine, D-penicillamine, and gold sodium thiomalate appeared to be related to renal involvement (Table 1). Granular deposits of immune complexes were seen by IF (Fig. 8a). However, most of the cases were graded early stage (stage I–II by Ehrenreich and Churg's classification) by EM (Fig. 8b), and some did not show a clear spike with PAM staining, which indicates a low level of glomerular basement membrane damage related to immune complex deposits.

Mesangial proliferative GN in RA

Mesangial proliferative GN was found in 21% of cases; IgA nephropathy was found in 12% and non-IgA GN in 9%. Only two of the 12 IgA nephropathy patients and none of nine non-IgA GN patients were men. IgA nephropathy tended to be seen in cases of relatively short-duration RA; in two cases, episodes of RA and IgA nephropathy occurred simultaneously, and in one case IgA nephropathy preceded RA. Mesangial proliferative GN presented intensive hematuria (grade 3.1 ± 1.2 in IgA nephropathy, 2.8 ± 1.2 in non-IgA GN), and less proteinuria (1.3 ± 1.6 g/day in IgA nephropathy, 1.0 ± 1.3 g/day in non-IgA GN), and few patients ($n = 3$) were nephrotic (one with IgA nephropathy and two with non-IgA GN). Renal function was normal (Cr 0.9 ± 0.3 mg/dl, Ccr 72.0 ± 24.4 ml/min). The serum level of IgA in IgA nephropathy was higher than that in non-IgA GN (505 ± 233 mg/dl vs. 243 ± 62 mg/dl).

Amyloidosis in RA

Amyloidosis was found in 11% of cases, and tended to be seen in older patients (age 62 ± 10 years) with long-duration RA (19 ± 11 years, range 5–41 years) and in an advanced stage of RA (3.8 ± 0.6). They presented less hematuria (grade 1.9 ± 1.1) but massive proteinuria (2.6 ± 1.3 g/day). Approximately half of them ($n = 5$) were nephrotic, and most of them ($n = 8$) developed renal failure (Cr 2.7 ± 3.1 mg/dl, Ccr 32.5 ± 23.9 ml/min).

Amyloid A (AA) deposits were stained in glomerulus and tubulus with Dylon (Fig. 9a) or Congo-red, but unstained after permanganate potassium treatment. EM (Fig. 9b) showed amyloid fibrils.

Interstitial nephritis in RA

Interstitial nephritis without glomerular abnormality was found in 9% of cases, which correlated with NSAIDs in four cases and lobenzarit disodium in two cases, and also with combined diseases (Sjögren syndrome in one case, SLE in one case, and one case with an undetermined etiology).

Eighty-two patients showed some tubulointerstitial changes (tubular atrophy, 73%; cell infiltration, 64%; interstitial fibrosis, 80%) that were seen in patients with long-duration RA.

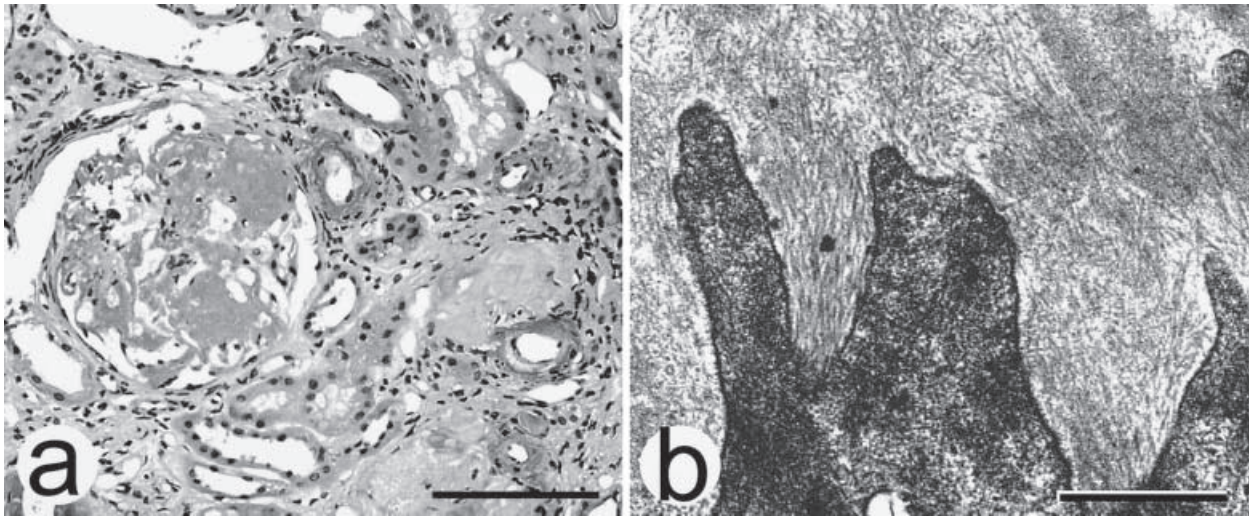

Fig. 9. Renal biopsy findings of amyloidosis in RA. **a** Dylon staining. Amyloid A depositions were stained in glomerulus and tubulus, but unstained after permanganate potassium treatment. *Bar* 100 μm. **b** Amyloid fibrils were detected by electron microscopy. *Bar* 1 μm

Table 2. Study on renal biopsies from more than 100 patients with RA

	Okayama[a]	Niigata[b]	Tampere[c]
Number of cases	100	158	110
Men : women	20 : 80	37 : 121	35 : 75
Membranous nephropathy	31%	31.0%	17.3%
Mesangial proliferative GN	21	34.2	36.4
(IgA nephropathy)	(12)	(19.6)	(7.3)
Minor changes	17	12.7	8.2
Amyloidosis	11	19.0	30.0
Crescentic GN	2	0.6	0
Interstitial nephritis	9	1.3	0.9

GN, glomerulonephritis
[a] Okayama University Medical School, Japan
[b] Niigata University Medical School, Japan
[c] Tampere University, Finland

Discussion

There have been many reports about renal lesions which seemed to be secondary complications to treatment with such DMARDs as gold[7,12,13] or D-penicillamine,[14,15] and discussions about the question of possible inherent renal lesions or "RA nephritis" which might be similar to lupus nephritis in SLE.[2,6,16] However, there are only two other large, published histopathological studies of renal biopsy specimens from over 100 patients with RA evaluated by LM, IF, and EM.[10,11] The results of the other two reports and our data are shown in Table 2.

In the other studies, the most common renal histology was mesangial proliferative GN, but in this study it was found in 21% of cases, and was second to membranous nephropathy. In RA, the production of such cytokines as interleukin-6, a growth factor of mesangial cells,[17] is increased.[18] Mesangial proliferative GN was considered to be a proper renal lesion in RA in some reports,[2,19,20] but the frequency of mesangial proliferative GN in RA is not higher than that in non-RA patients. The combination of IgA nephropathy and RA has been a particular concern owing to common pathogenetic bases such as HLA-DR4,[21,22] increased serum levels IgA,[23] and IgA-rheumatoid factor. Nakano et al.[24] failed to show any correlation between IgA nephropathy in RA and IgA-rheumatoid factor, and explained the difference in the frequency of IgA nephropathy in Japanese RA cases compared with frequencies reported by others workers (7.3% by Helin et al.[11]; 5% by Korpela et al.[25]) as being related to population bias.[10] Although serum levels of IgA in IgA nephropathy were higher than those in non-IgA GN, this study showed no significant correlation between the serum level of IgA and mesangial proliferation.

Gold thiomalate[12] and D-penicillamine[14] were the principal DMARDs related to most of the older cases of membranous nephropathy, and bucillamine[26] was related to the more recent cases. Bucillamine might be more likely to induce membranous nephropathy than gold thiomalate or D-penicillamine.[26] Most biopsy specimens of membranous nephropathy from bucillamine were early stage (stages I and II) examined by EM in this study, and some did not present clear spikes by PAM staining.[26] Therefore, renal morphological examinations should be performed by IF, EM, and LM.

In five cases of membranous nephropathy, the etiologies were unclear. There were several reports of membranous nephropathy in patients not treated with DMARDs (2 of 8 cases by Samuels et al.,[7] 4 of 14 cases by Honkanen et al.,[27] 9 of 49 cases by Nakano et al.,[10] and 1 of 19 cases by Helin et al.[11]). Membranous nephropathy was considered to be a proper renal lesion in RA by Samuels et al.[7] and Honkanen et al.,[27] but it is difficult to entirely rule out the influence of other factors. Even drugs such as NSAIDs[28] and hypotensive drugs have been reported to be causal agents for membranous nephropathy. Most cases of membranous nephropathy can be improved the causal DMARDs have

been stopped. If there is no improvement, other causes of secondary membranous nephropathy should be considered, such as membranous lupus nephropathy or malignancies. We had experience of a case which presented intractable nephrotic syndrome even after withdrawal of bucillamine, and was later revealed to be uterine cancer.

The reported incidence of amyloidosis in RA has been much higher than was found in this study. When the renal function of a patient is too poor to permit renal biopsy, amyloidosis can be diagnosed by extrarenal biopsies such as gastroduodenal mucosa, rectal mucosa, and fat tissue in the abdominal wall or minor salivary glands. However, the current study was limited to the renal biopsy, as were the studies of Helin et al.[11] and Nakano et al.[10] The incidence of renal amyloidosis in these three studies was found to be 11%, 30%, and 19%, respectively.

Amyloidosis was seen more frequently in patients with long-duration RA. In cases of vascular dominant deposition, proteinuria was less than in cases of glomerular dominant deposition. Many patients with renal amyloidosis developed renal failure (8 patients out of 11 patients). Even with dialysis therapy, their prognosis was poor due to cardiac failure from cardiac amyloidosis.

Although tubulointerstitial damage is an important lesion in patients with RA, it is sometimes undiagnosed because of the lack of proteinuria. Lobenzarit disodium is synthesized from anthranilic acid and is structurally similar to mefenamic acid, an NSAID. Two cases in this study developed renal failure without proteinuria, which indicates that renal disorder as a result of lobenzarit disodium might not be found by urinalysis.[29] The incidence of tubulointerstitial changes was very high in our study (82%), especially among patients with long-duration RA. NSAIDs are thought to be related to tubulo-interstitial changes.[30] Based on these facts, we recommend that testing for urinary abnormalities, including the elevation of urinary BMG and NAG, which are markers of tubular damage, should be routine in the examination of patients with RA.

In conclusion, the frequency of urinary abnormalities and renal dysfunction was high in RA patients. In cases of proteinuria during treatment with DMARDs, membranous nephropathy is the first possible diagnosis which should be suspected. In cases of hematuria, mesangial proliferative GN, including IgA nephropathy, is strongly suspected. In cases of proteinuria in patients with long-duration RA, amyloidosis should be the first diagnosis to be considered.

While it might seem reasonable to suspect the renal histological pattern from the clinical course, urinalysis, and renal functions of the patient, these relationships have not yet been established. Renal lesions in RA are very diverse, and the patterns of drug treatments are complex and varied within any large patient population, which makes the identification of causal relationships very difficult. Because membranous nephropathy and renal amyloidosis can be detected only by histological examinations, a renal biopsy should be performed in cases with any continuing urinary abnormality or a worsening of renal function.

References

1. Goronzy JJ, Weyand CM. Epidemiology, pathology and pathogenesis of rheumatoid arthritis. In: Klippel JH, Weyand CM, Wortmann RL, editors. Primer on the rheumatic diseases. 11th ed. Atlanta: Arthritis Foundation; 1997. p. 214–22.
2. Sellars L, Siamopoulos K, Wilkinson R, Leohapand T, Morley AR. Renal biopsy appearances in rheumatoid disease. Clin Nephrol 1983;20:114–20.
3. Yoshinaga Y, Nishiya K, Yamamura M, Hatano M, Ogura T, Takaoka M, et al. Study of urinary findings and renal functions in patients with rheumatoid arthritis (in Japanese). Kidney Dialysis 1989;26:477–82.
4. Symmons DP, Jones MA, Scott DL, Prior P. Long term mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol 1998;25:1072–7.
5. Yoshizawa H, Kudo H, Iwano K, Yamada A, Aikawa T, Miyamoto Y, et al. Causes of death in patients with rheumatoid arthritis: analysis of 117 cases in 13 years (in Japanese). Ryumachi 1990;30: 255–63.
6. Ota Z, Makino H. Drug-induced nephropathy in patients with rheumatoid arthritis (in Japanese). Clin Rheumatol 1990;3: 221–7.
7. Samuels B, Lee JC, Engleman EP, Hopper J. Membranous nephropathy in patients with rheumatoid arthritis: relationship to gold therapy. Medicine 1977;57:319–27.
8. Bender WL, Whelton A, Beschorner WE, Darwish MO, Hall-Craggs M, Solez K. Interstitial nephritis, proteinuria, and renal failure caused by nonsteroidal anti-inflammatory drugs: immunologic characterization of the inflammatory infiltrate. Am J Med 1984;76:1006–12.
9. Gertz MA, Kyle RA. Secondary systemic amyloidosis: response and survival in 64 patients. Medicine 1991;70:246–56.
10. Nakano M, Ueno M, Nishi S, Shimada H, Hasegawa H, Watanabe T, et al. Analysis of renal pathology and drug history in 158 Japanese patients with RA. Clin Nephrol 1998;50:154–60.
11. Helin HJ, Korpela MM, Mustonen J, Pasternack A. Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis Rheum 1995;38:242–7.
12. Ogura T, Takaoka M, Ogata R, Mino Y, Makino H, Hiramatsu M, et al. Clinical study of renal injury by gold therapy in patients with rheumatoid arthritis (in Japanese). Jpn J Clin Immun 1985;8:153–60.
13. Hall CL, Fothergill NJ, Blackwell MM, Harrison PR, MacKenzie JC, MacIver AG. The natural course of gold nephropathy: long-term study of 21 patients. Br Med J 1987;295:745–8.
14. Miyoshi A, Takaya Y, Kida K, Makino H, Hiramatsu M, Takahashi K, et al. D-penicillamine nephropathy. J Clin Electron Microsc 1980;13:55–62.
15. Hall CL, Jawad S, Harrison PR, MacKenzie JC, Bacon PR, Klouda PT, et al. Natural course of penicillamine nephropathy: a long-term study of 33 patients. Br Med J 1988;296:1083–6.
16. Mahallawy MN, Sabour MS. Renal lesions in rheumatoid disease. Lancet 1959;2:852–3.
17. Horii Y, Muraguchi A, Iwano M, Matsuda T, Hirayama T, Yamada H, et al. Involvement of IL-6 mesangial proliferative glomerulonephritis. J Immunol 1989;143:3949–55.
18. Kishimoto T. The biology of interleukin-6. Blood 1989;74:1–10.
19. Salmon MI, Gallo G, Poon TP, Goldblat MV, Tchertkoff V. The kidney in rheumatoid arthritis: a study based on renal biopsies. Nephron 1974;12:297–310.
20. Helin H, Korpela M, Mustonen J, Pasternack A. Mild mesangial glomerulopathy: a frequent finding in rheumatoid arthritis patients with hematuria or proteinuria. Nephron 1986;42:224–30.
21. Hiki Y, Kobayashi Y, Tateno S, Sada M, Kashiwagi N. Strong association of HLA-DR4 with benign IgA nephropathy. Nephron 1982;32:222–6.
22. Stastny P. Association of B-cell alloantigen Drw4 with rheumatoid arthritis. N Engl J Med 1978;298:869–71.
23. Barden J, Mullinax F, Waller M. Immunoglobulin levels in rheumatoid arthritis: comparison with rheumatoid factor titer, clinical stage and disease duration. Arthritis Rheum 1967;10:228–34.

24. Nakano M, Ueno M, Nishi S, Suzuki S, Hasegawa H, Watanabe T, et al. Determination of IgA- and IgM-rheumatoid factors in patients with rheumatoid arthritis with and without nephropathy. Ann Rheum Dis 1996;55:520–4.
25. Korpela MM, Mustonen J, Helin H, Pasternack A. Immunological comparison of patients with rheumatoid arthritis with and without nephropathy. Ann Rheum Dis 1990;49:214–8.
26. Nagakane T, Ogura T, Nishiya K, Natsumeda M, Haramoto T, Sasaki T, et al. Immuno-pathological study of bucillamine-induced nephropathy in patients with rheumatoid arthritis (in Japanese). Jpn J Clin Immunol 1990;13:346–55.
27. Honkanen E, Toernroth T, Petterson E, Skrifvars Bl. Membranous glomerulonephritis in rheumatoid arthritis not related to gold or D-penicillamine therapy: a report of four cases and review of the literature. Clin Nephrol 1987;27:87–93.
28. Sennesael K, Houte VD, Verbeelen. Reversible membranous glomerulonephritis associated with ketoprofen. Clin Nephrol 1986; 26:213–5.
29. Ota K, Makino H, Hayashi Y, Oishi T, Yamamura M, Nishiya K, et al. Two cases of interstitial nephritis in patients with rheumatoid arthritis induced by lobenzarit disodium (in Japanese). Clin Rheumatol 1994;5:265–71.
30. Levin ML. Patterns of tubulo-interstitial damage associated with nonsteroidal anti-inflammatory drugs. Semin Nephrol 1988;3:55–61.