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ORIGINAL ARTICLE

Significant association between renal function and area of amyloid deposition in kidney biopsy specimens in reactive amyloidosis associated with rheumatoid arthritis

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Abstract The kidney is a major target organ for systemic amyloidosis, resulting in proteinuria and an elevated serum creatinine level. In patients with reactive amyloidosis associated with rheumatoid arthritis, a correlation between the amount of amyloid deposits and clinical parameters is not known. The purpose of this study was to clarify the association between various factors including renal function and the area of amyloid deposition in these patients. Fifty-eight patients with an established diagnosis of reactive AA amyloidosis were studied. We retrospectively investigated the correlation between clinical data and the area occupied by amyloid in renal biopsy specimens. All the patients showed amyloid deposits in renal tissues, and the percentage of the area occupied by amyloid was <10% in 54 of them. Mesangial proliferative glomerulonephritis and membranous nephropathy were frequently combined with renal amyloidosis. For statistical analyses, the percentage of the area occupied by amyloid was transformed to a common logarithmic value (Log_{10} % amyloid), as the histograms showed a log-normal distribution. Log_{10} % amyloid was found to be correlated with age, creatinine (Cr) level, creatinine clearance (Ccr), blood urea nitrogen (BUN) level, and the estimated glomerular filtration rate (eGFR). Multiple linear regression analyses were then performed to examine the sex- and age-adjusted association between Log_{10} % amyloid and each of the clinical variables. Cr, Ccr, BUN, UA, CRP, and eGFR were significantly correlated with Log_{10} % amyloid, but urinary protein was not. There was a significant correlation between the area of amyloid deposition in renal tissue and parameters of renal function, especially Cr and Ccr. If amyloid deposition in renal tissue can be arrested or prevented, then it may be possible to maintain renal function at an acceptable level.

Keywords Rheumatoid arthritis · Reactive amyloidosis · Renal function · Renal biopsy

Introduction

Recently it has become apparent that rheumatoid arthritis (RA) is not only an inflammatory disease affecting multiple joints but also a cause of systemic organ dysfunction in relation to persistent systemic inflammation; this dysfunction may increase the risk of organ failure and death in affected patients [1–4]. Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of RA that arises from chronic, systemic, long-lasting inflammation, with elevated levels of serum AA (SAA) protein [5–7]. Serum AA is an acute-phase 12.5 kDa apolipoprotein associated with high-density lipoprotein and is the circulating precursor of amyloid A protein. Amyloid A fibrils are insoluble and can be deposited in systemic organs, including the kidneys, heart, or gastrointestinal (GI)

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tract, owing to the overproduction of SAA under such inflammatory conditions [6–8]. The prevalence of reactive AA amyloidosis in patients with RA is still unclear, but is no longer considered rare. The frequency of AA amyloidosis is associated with RA ranges from 7 to 26% [9–13], although the prevalence of clinically symptomatic amyloidosis is reportedly lower [14, 15]. Common clinical signs of reactive AA amyloidosis in patients with RA can be found by careful observation for the onset of proteinuria, kidney insufficiency, or GI tract symptoms, but amyloid deposition itself can be present before clinical signs of AA amyloidosis appear. This subclinical phase might explain the wide variation of disease prevalence.

Renal dysfunction is occasionally intractable, and some patients develop chronic renal failure and need to be started on dialysis. Renal failure is one of the important prognostic factors in patients with RA associated with reactive amyloidosis. The urinary abnormalities and renal dysfunction in patients with RA are thought to be induced by disease-modifying anti-rheumatic drugs (DMARDs) [16, 17], nonsteroidal anti-inflammatory drugs (NSAIDs) [18], and reactive amyloidosis [19]. Renal amyloidosis is one of the common causes of end-stage renal disease in RA patients. Previously published detailed studies of renal amyloidosis based on a large number of renal biopsy specimens have been limited [20–23]. In addition, the correlation between the amount of amyloidosis in the kidney and clinical parameters, including those related to renal function, is still not clear.

The purpose of the present study was to investigate an association between laboratory findings, including those related to renal function, and the area of amyloid deposits in the kidney in patients with reactive amyloidosis associated with RA.

Materials and methods

Patients

Fifty-eight patients with an established diagnosis of reactive AA amyloidosis participated in the study between January 1981 and December 2009. Each patient satisfied the 1987 American Rheumatism Association criteria for RA [24]. The study protocol was approved by the Institutional Review Board of Niigata University Hospital, and the subjects gave informed consent to participate, undergo renal biopsy, and the use and publication of the acquired data.

Diagnosis of reactive AA amyloidosis

All of the patients had undergone renal biopsy and had been confirmed to have reactive AA amyloidosis before study entry. The renal biopsies were performed using a fine needle under ultrasound guidance. The specimens were fixed in 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin, and cut into sections of 4-μm thick. The sections were stained with hematoxylin and eosin, periodic acid-Schiff, silver methenamine, and Masson trichrome for light microscopy for the evaluation of glomerular, interstitial, and vascular changes. Congo-red staining of renal tissue specimens was performed for histopathological diagnosis, and green birefringence was considered indicative of the presence of amyloid deposits. These deposits were confirmed as AA-type amyloid using two techniques: disappearance of Congo-red-positive staining after incubation with potassium permanganate and immunohistochemical analysis using anti-amyloid A antibody and anti-immunoglobulin light chain (AL) antibody to exclude AL amyloidosis. Electron microscopy had been performed previously for diagnostic purposes on glutaraldehyde-fixed, plastic resin-embedded tissues obtained by biopsy. One mm cubes of tissue were immediately fixed in 2.5% glutaraldehyde in 0.1 cacodylate buffer (pH 7.40) for 24 h. The tissue was then washed in phosphate buffer, post-fixed in aqueous osmium tetroxide, dehydrated and processed. An average basement membrane thickness of <250 nm was considered to be indicative of "thin basement membrane disease" (TBMD) as described previously [25].

Assessment

Clinical data were assessed from the patient records at the time of renal biopsy. Laboratory indices and clinical evaluation of disease activity included determinations of serum creatinine (Cr), 24 h proteinuria, 24 h creatinine clearance rate (Ccr), and C-reactive protein (CRP) level. Other clinical variables, such as total protein, albumin, BUN, uric acid (UA), and immunoglobulins, were assessed by routine laboratory methods. Ccr was corrected to a body surface area of 1.73 m^2. Estimated glomerular filtration rate (eGFR) was determined using the formula described previously [26].

Image analysis of amyloid-positive areas

Renal biopsy specimens were fixed in 10% formalin, embedded in paraffin, and cut into sections of 5-μm thick. Sections were considered suitable for the quantitative analysis. The amyloid-positive area in the renal tissue was determined on Congo-red-stained sections. One section of whole renal tissue was photographed. The borders of the amyloid-positive areas in each renal tissue section were traced in each photograph, excluding the tissue-free spaces. The total amyloid-positive area was measured with ImageJ v. 3.91 software (http://www.rsb.info.nih.gov/ij), and the average percentage of the amyloid-positive area per

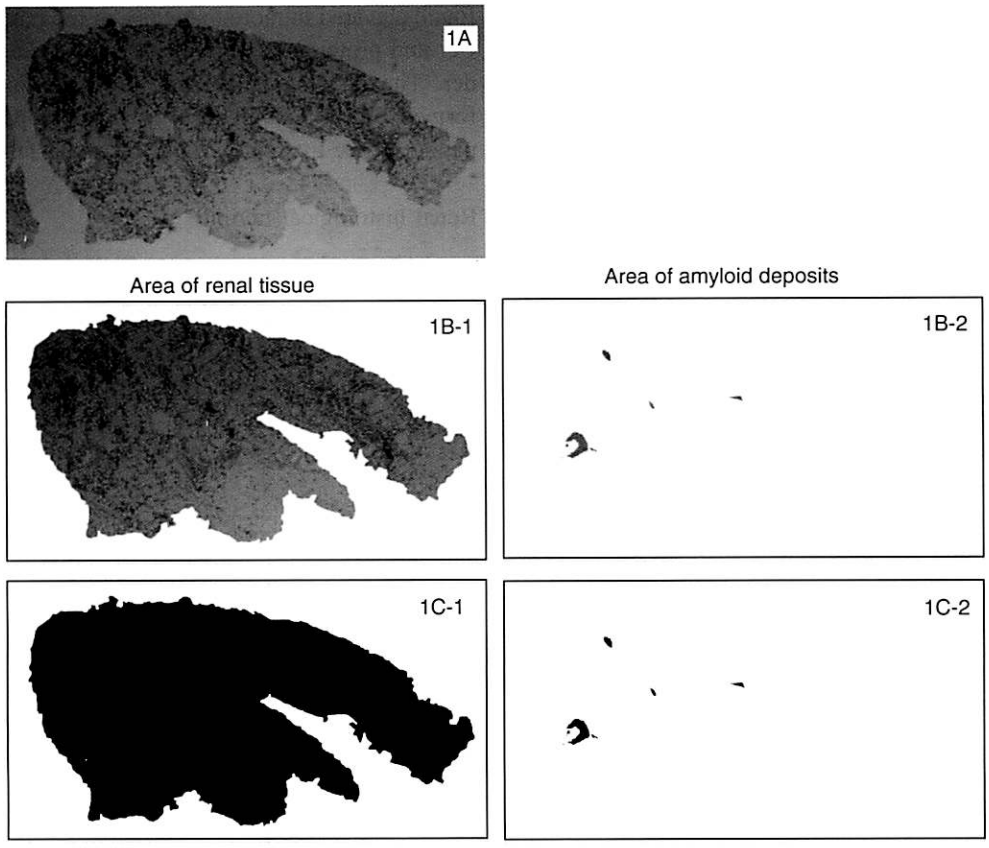

Fig. 1 *Image* analysis of renal tissue. **a** Original *image*. **b-1** *Image* trace around renal tissue. **b-2** *Image* trace around area of amyloid deposits. **c-1** Inversion of *image* trace of renal tissue to *black*. **c-2** Inversion of *image* trace to *black* to show amyloid deposits. % Amyloid area = (Area of amyloid deposits/Area of renal tissue) × 100

whole-tissue section was calculated. The process of image analysis is shown in Fig. 1.

Statistical analysis

For statistical analyses, the percentage area of amyloid deposition was transformed to a common logarithmic value (Log_{10} % amyloid), since the histograms showed a log-normal distribution (Fig. 2). Crude correlations between Log_{10} % amyloid and each of various clinical factors were tested using the Pearson correlation coefficient. Furthermore, multiple linear regression analysis was applied to assess the sex- and age-adjusted correlation between Log_{10} % amyloid and each clinical factor. All statistical analyses

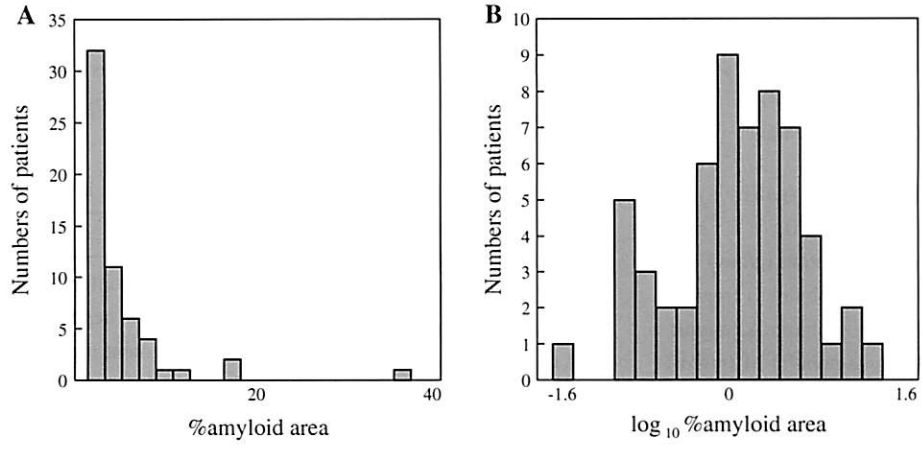

Fig. 2 Histogram showing distribution between number of patients and % amyloid area. **a** Distribution between number of patients and % amyloid area. The % amyloid area of 54 out of 58 patients was under 10%. Thirty-two out of 58 patients were under 2%. **b** Distribution between numbers of patients and Log_{10} % amyloid area. The distribution was similar to the normal probability distribution

were performed with SPSS ver. 13 for Windows (SPSS Inc, Chicago, IL, USA), and differences at $P < 0.05$ were considered statistically significant.

Results

Clinical features at the time of biopsy

Fifty-eight patients with renal AA amyloidosis associated with RA were evaluated in this study. Twelve patients were men and 46 were women. All of these patients had both symptomatic and asymptomatic signs of amyloidosis. Table 1 shows the clinical characteristics and laboratory findings of these patients at the time amyloidosis was diagnosed. Low levels of serum albumin were frequent. Values of inflammatory parameters such as CRP were found elevated in more than 90% of the patients. Abnormal Ccr and proteinuria were also frequent due to renal disorder. The histological diagnosis of amyloidosis was performed by the examination of renal biopsy samples. All patients were treated with NSAIDs and DMARDs.

Table 1 Clinical characteristics of patients enrolled in this study

Characteristic	
Male/female, *n*	12/48
Mean age at RA onset, years (SD) [range]	44.3 (11.6) [15–70]
Mean age at amyloidosis onset, years (SD) [range]	58.2 (11.7) [28–75]
Mean duration between RA and amyloidosis onset, years (SD) [range]	13.9 (7.9) [2–34]
Stage	*n* (%)
I	0 (0)
II	2 (3.4)
III	12 (20.7)
IV	44 (75.9)
Class	*n* (%)
1	6 (6.9)
2	35 (60.4)
3	17 (29.3)
4	2 (3.4)
CRP (mg/dl)	4.2 (2.2) [0.3–1.0]
BUN (mg/dl)	24.1 (10.5) [10.0–70.8]
Serum creatinine (mg/dl)	1.2 (0.9) [0.5–5.7]
Uric acid (mg/dl)	6.1 (2.1) [1.9–12.1]
Creatinine clearance (ml/min/1.73 m^2)	56.9 (27.0) [12.7–131.5]
Total protein (g/dl)	7.5 (10.1) [3.8–7.7]
Albumin (g/dl)	3.0 (0.8) [1.3–4.1]
Urinary protein (g/day)	2.0 (1.9) [0–7.9]
Immunoglobulin G (mg/dl)	1,763.0 (572.3) [3,263.4–242.0]
Immunoglobulin A (mg/dl)	348.1 (161.9) [83.0–637.0]
Immunoglobulin M (mg/dl)	198.1 (157.3) [291–531.1]

SD standard deviation, *CRP* C-reactive protein, *BUN* blood urea nitrogen

Renal histological findings

All of the patients had amyloid deposits in renal tissue. Other additional histological findings are shown in Table 2. Mesangial proliferative glomerulonephritis and membranous nephropathy were frequently combined with renal amyloidosis. Thin basement membrane disease (TBMD) was also frequent, as detected by electron microscopy.

Distribution between numbers of patients and % amyloid area

Histograms between numbers of patients and % amyloid area are shown in Fig. 2a. The percent amyloid area in 54 out of 58 patients was under 10% while 32 out of 58 patients were under 2%. Because the % amyloid area was unevenly distributed, we analyzed the distribution between numbers of patients and Log_{10} % amyloid area. This result is shown in Fig. 2b. The distribution was similar to normal probability distribution.

Correlation between Log_{10} % amyloid and variables

The correlation between Log_{10} % amyloid and selected clinical factors is shown in Fig. 3. Patient age ($r = -0.293$, $P = 0.027$, Fig. 3a), Ccr ($r = -0.554$, $P < 0.001$, Fig. 3c), eGFR ($r = -0.555$, $P < 0.001$, Fig. 3g), and CRP ($r = -0.653$, $P = 0.008$, Fig. 3h) showed a significant negative correlation with Log_{10} % amyloid, whereas Cr ($r = 0.503$, $P < 0.001$, Fig. 3b) and BUN ($r = 0.153$, $P = 0.286$, Fig. 3d) showed a significant positive correlation. UA (Fig. 3e) and urinary protein (Fig. 3g) were not significantly correlated with Log_{10} % amyloid. We also analyzed correlations with other clinical factors such as sex (male = 0, female = 1), and the serum concentrations of sodium, potassium, total protein, albumin, immunoglobulins [immunoglobulin G (IgG), immunoglobulin A (IgA),

Table 2 Renal histological findings of amyloid patients

Renal histological findings	Number of patients (%)
Mesangial proliferative glomerulonephritis	13 (22.4)
Membranous nephropathy	6 (10.3)
Thin basement membrane disease	6 (10.3)
Interstitial nephritis	4 (6.9)
Crescentic glomerulonephritis	2 (3.4)

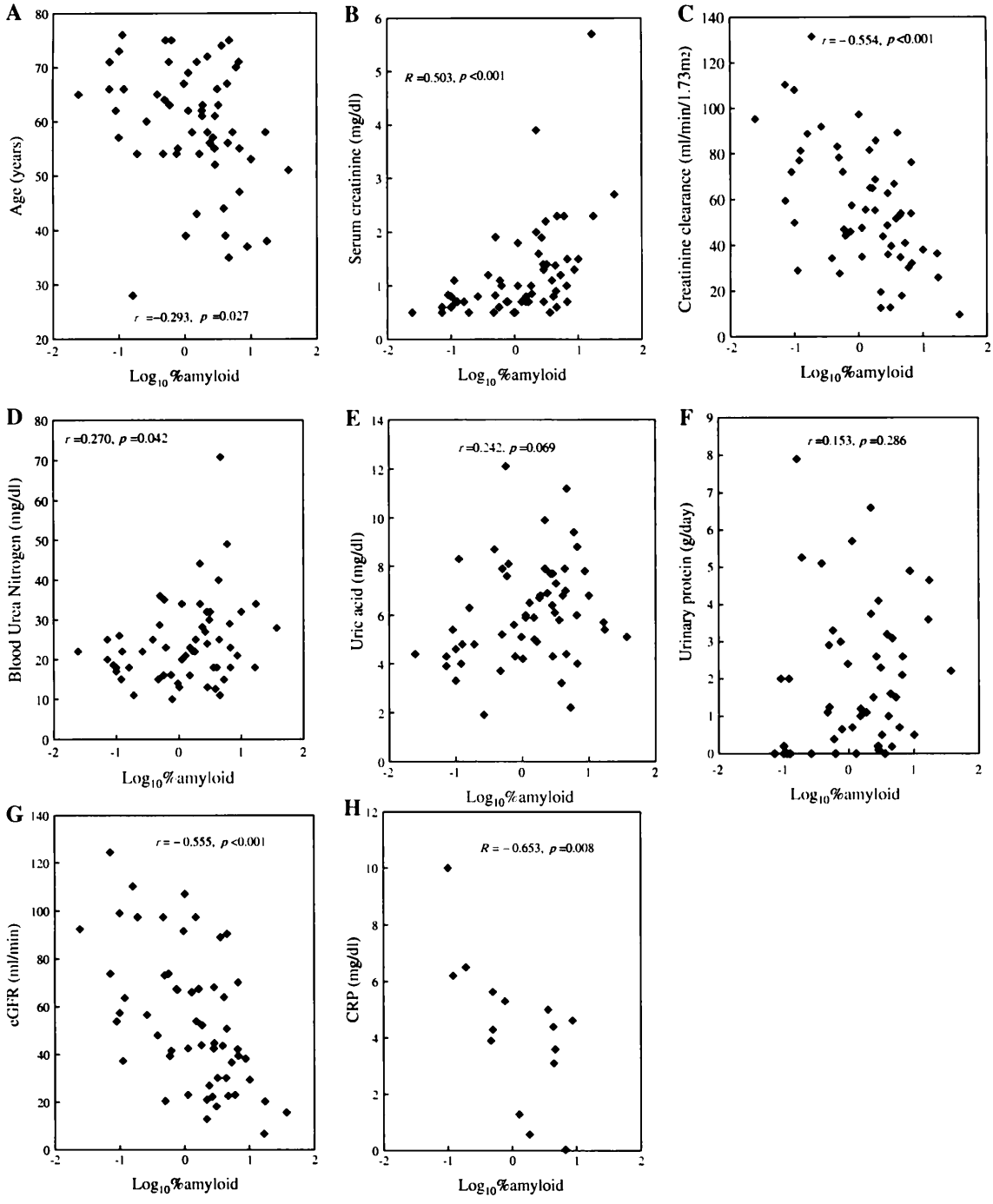

Fig. 3 Correlation between Log_{10} % amyloid and variables. **a** Correlation between Log_{10} % amyloid and age. **b** Correlation between Log_{10} % amyloid and Cr. **c** Correlation between Log_{10} % amyloid and creatinine clearance. **d** Correlation between Log_{10} % amyloid and BUN. **e** Correlation between Log_{10} % amyloid and uric acid. **f** Correlation between Log_{10} % amyloid and urinary protein. **g** Correlation between Log_{10} % amyloid and eGFR. **h** Correlation between Log_{10} % amyloid and CRP. The age of the patient significantly correlated with Log_{10} % amyloid. Cr and Ccr showed strong correlation with Log_{10} % amyloid. BUN showed significant correlation with Log_{10} % amyloid but UA and urinary protein did not correlate with Log_{10} % amyloid. CRP showed inverse correlation with Log_{10} % amyloid

and immunoglobulin M (IgM)], complement components (C3, C4), and total hemolytic component (CH 50). We found none of these factors to be significantly correlated with Log_{10} % amyloid.

Sex- and age-adjusted multiple linear regression analyses showed that Log_{10} % amyloid had a significant positive association with Cr and a significant negative association with Ccr, eGFR, and CRP, by crude correlation analysis

Table 3 Sex- and age-adjusted association between Log_{10} % amyloid and each clinical variable

	Regression coefficient (95% CI)	*P* value
Serum creatinine (mg/dl)	0.76 (0.46–1.07)	<0.001
Creatinine clearance (ml/min/1.73 m^2)	−25.7 (−33.6 to −17.8)	<0.001
Blood urea nitrogen (mg/dl)	6.75 (3.49–10.01)	<0.001
Serum uric acid (mg/dl)	1.08 (0.36–1.80)	0.005
Urinary protein (g/day)	0.18 (−0.62 to 0.99)	0.655
eGFR (ml/min)	−27.7 (−36.1 to −19.3)	<0.001
CRP (mg/dl)	−2.33 (−4.31 to −0.35)	0.025

Regression coefficient shows the effect of Log_{10} % amyloid on each clinical factor adjusted for sex and age by multiple linear regression analysis. *eGFR* estimated glomerular filtration rate

(Table 3). Furthermore, Log_{10} % amyloid appeared to have a significant positive association with BUN ($P < 0.001$) and UA ($P = 0.005$) when the effects of sex and age were adjusted for.

Discussion

End-stage renal disease and GI disease, including intractable diarrhea, are well-known complications in RA patients with AA amyloidosis and are considered major causes of death [27–32]. The survival rate of RA patients with AA amyloidosis receiving hemodialysis is known to be extremely poor in comparison with that of patients with other kidney diseases [32–35]. Simultaneously, intractable diarrhea is reported to have a poor prognosis in such patients once it has developed [30]. Prevention or treatment of these complications is therefore a critical issue. There have been several attempts to establish an effective protocol for the treatment of reactive AA amyloidosis associated with RA, including the use of corticosteroids and immunosuppressants to control RA disease activity and to improve kidney function and overall patient survival.

Some reports have suggested that the patients with AA amyloidosis have laboratory signs of inflammation, with significantly increased plasma levels of acute-phase proteins such as CRP [13, 30]. In our patients, there was high disease activity during the clinical course of RA. Our data showed that CRP and Log_{10} % amyloidosis had a negative correlation. These data seemed to be interesting because we usually perform GI biopsy as a screening tool. If amyloid is detected for GI biopsy, we usually increase anti-inflammatory treatment. After that, renal biopsy is performed. This might be the reason for the unexpected result. It is important to note that our patients experienced mild azotemia, and the depression of Ccr was frequent thus indicating renal insufficiency. Urinary abnormalities (proteinuria and hematuria) were also common, and such abnormalities and renal dysfunction in RA are known to be induced by DMARDs [16, 36], NSAIDs [18], and secondary amyloidosis [19].

Our amyloidosis patients had received many DMARDs during treatment for RA. Previous studies have shown that the most common feature of renal histology is mesangial proliferative GN. In the present study, this was found in 22.6% of cases, being second in frequency to membranous nephropathy. In RA, the production of cytokines such as interleukin-6, a growth factor for mesangial cells [37], is increased [38]. Mesangial proliferative GN has been considered to be a common renal lesion in RA in some reports [39, 40], 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 conditions such as HLA-DR4 [41, 42] and increased serum levels of IgA [43]. Gold thiomalate [44] and D-penicillamine [45] were the principal DMARDs related to most of the older cases of membranous nephropathy, whereas bucillamine [46] was related to the more recent cases. Bucillamine might be more likely to induce membranous nephropathy than gold thiomalate or D-penicillamine [46]. Most biopsy specimens of tissue showing bucillamine-related membranous nephropathy showed early-stage (stages I and II) disease, as examined by EM in this study, and some did not present clear spikes by PAM staining (stage I) [46]. All of our patients with membranous nephropathy had been treated with gold sodium thiomalate, D-penicillamine, or bucillamine. Membranous nephropathy is well known to cause nephrotic syndrome. TBMD has been frequently observed in RA patients, and abnormalities of the glomerular basement membrane (GBM) are closely related to the presence of hematuria without proteinuria [25]. We have previously found that about 70% of RA patients who underwent renal biopsy showed proteinuria and that 60% of them showed hematuria [20]. It is known that RA causes some defects in collagen production or metabolism, and the effects of NSAIDs or DMARDs on TBMD have not been fully investigated. These additional renal diseases may confuse the overall picture or partially conceal the severity of renal amyloidosis. Although, the severity of renal amyloidosis is difficult to determine, we consider that the percentage area occupied by amyloidosis in renal tissue is an important marker. Recently, therapy with biological agents such as anti-TNF and anti-IL-6 has been developed against a background of increased understanding of the pathogenesis of rheumatoid arthritis (RA), representing a tremendous advance in the management of RA. We have reported that anti-TNF therapy results in rapid removal and sustained disappearance of amyloid deposits in gastric

mucosal tissue with amelioration of renal function [47]. Accordingly, we speculated that the rapid removal of amyloid deposits from renal tissue might ameliorate renal function. However, the correlation between the amount of amyloidosis in the kidney and clinical parameters including renal function has not been clear. As a first step, it is important to clarify the correlation between the amount of amyloidosis and clinical parameters in patients with reactive amyloidosis due to RA. In most of our patients, the percentage area of renal tissue occupied by amyloid was <10%. The patients with amyloidosis underwent renal biopsy at a relatively early stage. To clarify the correlation of many clinical parameters with the percentage area occupied by amyloid, we used Log_{10} % amyloid area for analysis.

Serological indices such as Cr and BUN were significantly correlated with Log_{10} % amyloid as was Ccr. Furthermore, calculated renal function in terms of eGER was also significantly correlated. However, urinary protein did not show a correlation, despite the fact that most clinicians believe that urinary protein is an important marker of renal amyloidosis. Apart from renal amyloidosis, baseline renal disease, such as membranous nephropathy, may affect the level of urinary protein excretion. Additionally, in AA amyloidosis, renal amyloid is frequently deposited in order, starting inside the GBM and mesangium. Amyloid deposits may occur in a segmental, diffuse mesangial, nodular or pure basement membrane pattern [48]. Segmental amyloid deposits are small, discrete, and confined to the mesangium without formation of nodules. Although, this form is very small, it has been pointed out that it can be associated with massive proteinuria. In our study, these small nodules were included in the amyloid-positive area and may have been the reason for massive proteinuria. This might be the reason why Log_{10} % amyloid was not correlated with urinary protein. We also examined the sex- and age-adjusted association between Log_{10} % amyloid and each clinical variable using multiple linear regression analysis. The levels of UA, Cr, BUN, Ccr, and eGFR were significantly correlated, and the levels of BUN and UA reflected renal function. Recently, SAA alleles were reported to be a major risk factor in the progression of systemic amyloidosis. These parameters are considered to be correlated with quality of amyloidosis [49]. Localization of amyloidosis is also considered to be an important factor associated with renal insufficiency. However, we could not show these relationships between these parameters in our limited conditions. Nonetheless, these analyses must be done but with a large population of patients as the next step.

In conclusion, there is a significant correlation between the percentage area of amyloid deposition in renal tissue and renal function, especially in terms of Cr and Ccr. Urinary protein is an important marker of the extent of renal amyloidosis, but is not correlated with the percentage area of amyloid deposition because of other forms of underlying renal disease. Therefore, prevention of amyloid deposition in renal tissue may help to maintain renal function. Recently, therapies with biologic agents such as anti-TNF and anti-IL-6 have become standard for DMARD-resistant RA patients, and might also become a routine strategy for amyloidosis patients with RA.

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Conflict of interest None of the authors has a conflict of interest to declare.

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