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ORIGINAL ARTICLE

Association between clinical parameters and amyloid-positive area in gastroduodenal biopsy in reactive amyloidosis associated with rheumatoid arthritis

Takeshi Kuroda · Naohito Tanabe · Daisuke Kobayashi · Hiroe Sato · Yoko Wada · Shuichi Murakami · Masaaki Nakano · Ichiei Narita

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Abstract Our study was aimed to clarify an association between gastrointestinal (GI) amyloid-positive area and various kinds of factors including renal function in reactive amyloidosis associated with rheumatoid arthritis (RA). Twenty-five patients with an established diagnosis of reactive AA amyloidosis participated in the study between January 1989 and December 2009. Each patient satisfied the 1987 American Rheumatism Association criteria for RA. All patients showed amyloid deposits in both of GI and renal tissues. The average amyloid-deposited area was 2.2% in renal tissues and 3.7% in GI tissues although the difference was not statistically significant. Twenty-two patients out of 25 patients showed less than 5% of amyloidosis in renal tissues and nineteen patients showed 5% of amyloidosis in GI tissues. In 5 out of a total of 25 cases, the amyloid-deposited area in GI tissues was lesser than that in renal tissues. Mesangial proliferative glomerulonephritis, thin basement membrane disease (TBMD) and membranous nephropathy were frequently combined with renal amyloidosis. For statistical analyses, renal and GI tissues of % amyloid-positive areas were transformed to common logarithmic values (Log_{10}%amyloid), since the histograms showed log-normal distribution. Clinical data were assessed by patient record at the time of GI biopsy. The correlation between Log_{10}%GI-amyloid and age, creatinine (Cr), creatinine clearance (Ccr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) were not significantly associated with Log_{10}%GI-amyloid in crude correlation analyses and also in sex- and age-adjusted linear regression analyses. Although GI biopsy was not correlated with clinical factors, GI amyloid-positive areas were larger than renal amyloid-positive areas. Endoscopic screening of the upper GI tract is common in Japan, and amyloid-deposited area in GI tissues was sufficient to use for the diagnosis of amyloidosis compared with renal tissues in terms of convenience and sensitivity.

Keywords Arthritis-rheumatoid · Reactive amyloidosis · Gastroduodenal biopsy

T. Kuroda (✉)
Niigata University Health Administration Center,
2-8050 Ikarashi, Nishi-ku, Niigata City 950-2181, Japan
e-mail: kurodat@med.niigata-u.ac.jp

N. Tanabe
Division of Health Promotion, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Cyuuou-ku, Niigata City 951-8510, Japan

D. Kobayashi · H. Sato · Y. Wada · S. Murakami · I. Narita
Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Cyuuou-ku, Niigata City 951-8510, Japan

M. Nakano
Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, 2-746 Asahimachi-Dori, Cyuuou-ku, Niigata City 951-8518, Japan

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 due 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 and

long-lasting inflammation, with elevated levels of serum AA (SAA) protein [5–7]. SAA 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) 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 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.

In recent years, GI biopsy has been recommended owing to the higher incidence of amyloidosis [16–18]. Endoscopic screening of the upper GI tract is common in Japan. Previous publications reported no complications related to the procedure [9]. Some patients with GI amyloidosis had a high rate of renal insufficiency, shown by proteinuria, haematuria, elevation of serum creatinine and depression of creatinine clearance (Ccr). Even in patients who lack these findings, amyloid may be deposited in renal tissue. It is difficult to diagnose amyloidosis according to renal function and urinary findings. In addition, anti-inflammatory drugs may cause interstitial nephritis and papillary necrosis, leading to renal failure. Obana et al. [19] reported that more than 82% of RA patients with GI amyloidosis had azotaemia. In our study, renal dysfunction is occasionally intractable, and some patients develop chronic renal failure and initiated dialysis. Renal failure is an important prognostic factor in patients with RA with reactive amyloidosis. The urinary abnormalities and renal dysfunction in RA are thought to be induced by disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drags (NSAIDs) [20, 21] and reactive amyloidosis [22]. Renal amyloidosis is one of the common causes of end-stage renal disease (ESRD) in RA patients. As published, detailed studies based on large numbers of renal biopsy specimens of renal amyloidosis are limited [22–24]. Additionally, the correlation between the amount of amyloidosis in the kidney, GI tissue and clinical parameters including renal function is yet unclear.

Our purpose was to investigate the association between laboratory findings at GI biopsy, GI amyloid–deposited area and renal amyloid–deposited area in reactive amyloidosis associated with RA.

Materials and methods

Patients

Twenty-five patients with an established diagnosis of reactive AA amyloidosis participated in the study between January 1989 and December 2009. Each patient satisfied the 1987 American Rheumatism Association criteria for RA [25]. The study protocol was approved by the Institutional Review Board of Niigata University Hospital, and the subjects gave informed consent to participate for renal biopsy, Gl biopsy and to use acquired data.

Diagnosis of reactive AA amyloidosis

All patients had renal biopsy and GI biopsy, which had been confirmed to have reactive AA amyloidosis before they entered the study. Upper GI endoscopy was performed on each patient, regardless of the presence or absence of GI symptoms, to obtain biopsy specimens. A forward-viewing instrument (models GIF-Q10 or Q20: Olympus, Tokyo) was used. Biopsy specimens were obtained from the lesser curvature of the gastric antrum, the bulbus, and the second portion of the duodenum using biopsy forceps (FB-24Q, Olympus, Tokyo), regardless of the presence or absence of abnormalities on endoscopy. These biopsy specimens were fixed in 10% formalin, embedded in paraffin and sectioned at 5-μm intervals. The sections were subsequently stained with haematoxylin–eosin (HE) and Congo red. Amyloid deposits were detected with Congo red and showed green birefringence under polarization microscopy. The renal biopsies were performed under ultrasound-guided needle biopsy. The specimens were fixed in 10% phosphate-buffered formalin (pH 7.2), embedded in paraffin and cut into 4-μm sections. The sections were stained with haematoxylin and eosin, periodic acid Schiff, silver methenamine and Masson trichrome stains for light microscopy to evaluate the 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 2 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 on glutaraldehyde-fixed, plastic resin-embedded tissue had been performed previously for diagnostic purposes on biopsy tissues. One-millimetre 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 as described for electron microscopy. The interval between GI biopsy and renal biopsy was within 2 months.

Assessment

Clinical data were assessed by patient record at the time of GI biopsy. Laboratory index 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). Other clinical variables, such as total protein, albumin, blood urea nitrogen (BUN), uric acid (UA) and immunoglobulins, were assessed by routine laboratory method. Estimated glomerular filtration rate (eGFR) was estimated by the formula described previously [26].

Image analysis of amyloid-positive areas

The renal and GI biopsy specimens were fixed in 10% formalin, embedded in paraffin, and cut into 5-μm-thick sections. Sections were considered suitable for quantitative analysis if they consisted of the full thickness of the mucosa with vascular components and were cut perpendicular to the surface. The amyloid-positive area in the renal tissue was determined on the Congo-red-stained sections. One section of whole renal and GI tissue was photographed. The borders of the amyloid-positive areas in each renal tissue were traced in each photograph, excluding the tissue-free spaces. The total amyloid-positive area was measured with ImageJ v. 3.91 software (http://rsb.info.nih.gov/ij), and the percentage of amyloid-positive area per whole-tissue section was calculated. All selected slides were evaluated for total amyloid-positive area, and the highest percentage of amyloid-positive area in each biopsy sample was selected for analysis.

Statistical analysis

For statistical analyses, both GI and renal %amyloid-positive areas were transformed to common logarithmic values (Log_{10}%amyloid) since both of the histograms showed log-normal distribution (Figs. 1, 2). Crude correlation between

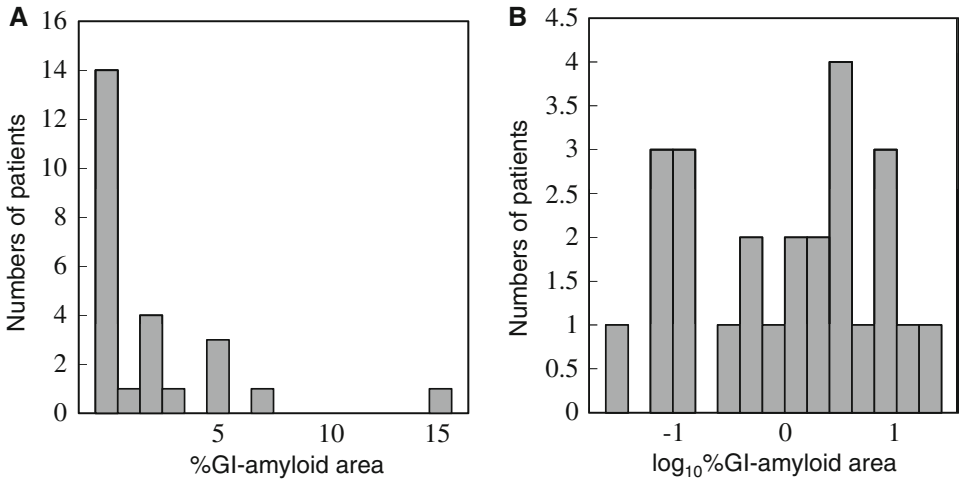

Fig. 1 Histogram showing distribution between numbers of patients and % gastrointestinal (GI)-amyloid area. **a** Distribution between numbers of patients and %GI amyloid area. Nineteen patients out of 25 patients showed less than 5% of amyloidosis in GI tissues. **b** Distribution between numbers of patients and Log_{10}%GI-amyloid area. The distribution was similar to normal probability distribution

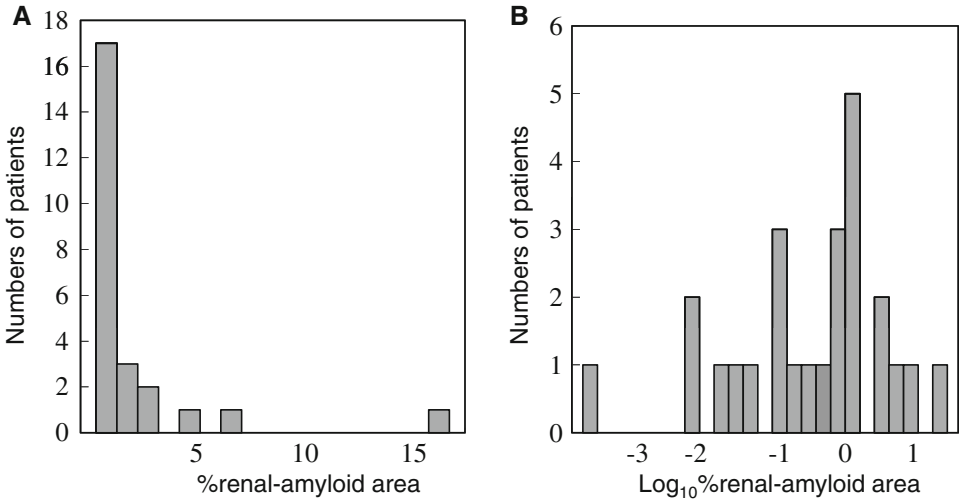

Fig. 2 Histogram showing distribution between numbers of patients and % renal-amyloid area. **a** Distribution between numbers of patients and % renal-amyloid area. Twenty-three patients out of 25 patients showed less than 5% of amyloidosis in GI tissues. **b** Distribution between numbers of patients and Log_{10}% renal-amyloid area. The distribution was similar to normal probability distribution

Log_{10}%GI-amyloid and each clinical factor was tested using a Pearson's correlation coefficient or Spearman's ρ. Furthermore, multiple linear regression analysis was applied to assess the sex- and age-adjusted effect of Log_{10}%GI-amyloid on each clinical factor. All statistical analyses were performed with SPSS ver. 13 for Windows (SPSS Inc, Chicago, IL, USA) and a P value < 0.05 was considered statistically significant.

Results

Clinical features at the time of biopsy

Twenty-five patients with renal AA amyloidosis associated with RA were evaluated in this study. Seven patients were male and 18 were female. All of these patients had both symptomatic and asymptomatic signs for amyloidosis. Table 1 shows the clinical characteristics and laboratory findings of these patients at the time of diagnosing GI amyloidosis was assessed. Low levels of serum albumin were frequent. Abnormal Ccr, BUN and proteinuria were also frequent due to renal disorder. Consequently, eGFR was depressed in 68% of these cases. All patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs).

Renal and gastrointestinal histological findings

All of our patients had amyloid deposits in both the GI and renal tissues. The average amyloid-deposited area was 2.2% in renal tissues and 3.7% in GI tissues, but these values were not statistically significant. Twenty-two patients out of 25 patients showed less than 5% of amyloidosis in renal tissues, and nineteen patients showed less than 5% of amyloidosis in GI tissues. There were 5 cases out of a total of 25 cases, whose amyloid-deposited area in GI tissues were found to be lesser than that in renal tissues. Other additional renal histological findings are shown in Table 2. Mesangial proliferative glomerulonephritis was frequently combined with renal amyloidosis. Thin basement membrane disease (TBMD) detected by electron microscopy and membranous nephropathy were also observed.

Correlation between Log_{10}%GI-amyloid and clinical characteristics

The correlation between Log_{10}%GI-amyloid and selected clinical factors are shown in Table 3. All the characteristics,

Table 1 Clinical characteristics of patients enrolled in study

Characteristics	Minimum	Maximum	Average	SD	%> abnormal (criterion)
%Renal-amyloid	0.0245	16.7	2.20	3.55	
Log_{10}%Renal-amyloid	−1.61	1.22	−0.07	0.66	
%GI-amyloid	0.0146	15.11	2.21	3.44	
Log_{10}%GI-amyloid	−1.84	1.18	−0.30	0.91	
Systolic Blood Pressure (mmHg)	110	168	134.3	13.6	68(≦140)
Diastolic Blood Pressure (mmHg)	60	102	76.0	8.8	4 (≦90)
Urinary protein (g/day)	0	5.7	1.83	1.83	88 (<0.1)
Creatinine clearance (mL/min/1.73 m^2)	27.7	131.5	59.4	25.8	75 (≧80.0)
Blood urea nitrogen (mg/dL)	10	36	22.0	7.3	80 (8–20)
Creatinine (mg/dL)	0.5	5.7	1.13	1.06	24 (0.5–1.1)
Uric acid (mg/dL)	3.7	8.8	5.98	1.65	28 (2.9–7.5)
Na (mEq/L)	14	148	136.7	25.7	0 (134–147)
K (mEq/L)	2.7	4.9	4.0	0.8	4 (3.3–4.8)
Total protein (g/L)	4.7	7.2	6.2	0.7	64 (6.6–8.0)
Albumin (g/L)	1.83	3.93	3.1	0.6	100 (4.1–5.0)
Immunoglobulin G (mg/dL)	666	3,263.4	1,441.4	488.7	20 (870–1,700)
Immunoglobulin A (mg/dL)	117	932	391.8	185.3	64 (110–410)
Immunoglobulin M (mg/dL)	74	531.1	200.7	121.3	64 (35–220)
C3 (mg/dL)	45.2	140.6	85.8	21.2	8 (65–135)
C4 (mg/dL)	16	53.2	32.1	9.1	32 (13–35)
CH50 (U/mL)	18.7	51.9	43.3	10.8	20 (28–53)
eGFR (mL/min/1.73 m^2)	6.7	124.4	62.5	31.0	68 (>80.0)
Age (years old)	39	76	61.6	9.7	

Table 2 Renal histological findings of amyloid patients

Renal histological findings	Number of patients (%)
Mesangial proliferative glomerulonephritis	9 (36)
Thin basement membrane disease	4 (16)
Membranous nephropathy	3 (12)
Interstitial nephritis	2 (8)

such as patient sex, age, Ccr, BUN, Cr, UA, urinary protein, complements and eGFR, showed no significant correlation with Log_{10}%GI-amyloid. Log_{10}%GI-amyloid was not associated with any of these clinical factors also in sex- and age-adjusted analyses (Table 4).

Discussion

The frequency of amyloidosis in RA has been reported in the range of 5–13.3% in cases confirmed by biopsy and 14–26% in cases confirmed by autopsy [9, 12]. We previously presented a 7.1% incidence among a group of patients with long disease duration, high anatomical class and high disease activity [13]. Patients with RA gastric ulcer and erosion are common because of their use of steroids and NSAIDs. Upper digestive symptoms, such as anorexia, nausea and vomiting, and lower digestive symptoms, such as constipation and diarrhoea, are also common in patients with GI amyloidosis. In recent years, amyloid deposition has been ascertained by biopsies of various organs [27, 28]. Rectal biopsy has been widely used as a diagnostic procedure because amyloid deposition frequently occurs in the digestive tract [29, 30]. Rectal or abdominal fat aspiration biopsy has been described as the procedure of choice for diagnosing systemic amyloidosis. GI biopsy is recommended owing to the higher incidence of amyloidosis [16–18]. Endoscopic screening of the upper GI tract is common in Japan. Previous publications reported no complications related to endoscopy [9], and we also encountered no complications.

Some patients with GI amyloidosis have a high rate of renal insufficiency, as shown by proteinuria, haematuria, elevation of serum creatinine and depression of Ccr. Even in patients who lack these findings, amyloid may be deposited in renal tissue. It is difficult to diagnose amyloidosis according to renal function and urinary findings. As all of our amyloid patients were treated with NSAIDs and DMARDs, haematuria and proteinuria might have been induced by these drugs [20, 21]. Also, recent reports show that thin basement membrane disease and mesangioproliferative

Table 3 Correlation between Log10%GI-amyloid and clinical characteristics

Characteristics	Statistics	r or ρ	P-value
Sex, n(%) of women	18 (72.0)	0.17*	0.408
Age (years old)	61.560 ± 9.721	−0.06	0.763
%GI-amyloid median (IQR)	0.611 (0.05, 2.92)	–	–
Log10%GI-amyloid	−0.304 ± 0.911	–	–
%Renal-amyloid median (IQR)	0.97 (0.43, 2.75)	0.20*	0.345
Log10%Renal-amyloid	−0.071 ± 0.670	0.22	0.287
Systolic blood pressure (mmHg)	134.3 ± 13.7	–	–
Diastolic blood pressure (mmHg)	76.0 ± 8.9	−0.09	0.678
Urinary protein (g/day)	1.8 ± 1.8	−0.07	0.771
Creatinine clearance (mL/min/1.73 m^2)	59.4 ± 25.8	0.18	0.412
Blood urea nitrogen (mg/dL)	22.0 ± 7.3	−0.27	0.197
Creatinine (mg/dL)	1.1 ± 1.1	0.05	0.808
Uric acid (mg/dL)	6.0 ± 1.6	−0.19	0.362
Na (mEq/L)	136.7 ± 25.7	0.09	0.664
K (mEq/L)	4.0 ± 0.8	0.20	0.330
Total protein (g/L)	6.2 ± 0.7	0.18	0.377
Albumin (g/L)	49.7 ± 12.6	−0.16	0.443
Immunoglobulin G (mg/dL)	1,441 ± 489	0.23	0.279
Immunoglobulin A (mg/dL)	392 ± 185	0.10	0.623
Immunoglobulin M (mg/dL)	200.7 ± 121.3	0.36	0.077
C3 (IU/mL)	85.8 ± 21.2	0.08	0.695
C4 (IU/mL)	32.1 ± 9.1	−0.08	0.717
CH50 (U/mL)	65.6 ± 104.4	−0.14	0.558
eGFR (mL/min/1.73 m^2)	62.6 ± 31.6	0.10	0.629

Statistics are mean ± SD otherwise noted

IQR interquartile range, *r* Pearson's correlation coefficient or *Spearman's ρ with Log_{10}%GI-amyloid

Table 4 Sex- and age-adjusted association with Log10%GI-amyloid

Characteristics	*B*	(SE)	*P*
Age (years old)	0.277	(0.309)	0.380
Systolic blood pressure (mmHg)	−0.025	(0.017)	0.149
Diastolic blood pressure (mmHg)	−0.001	(0.027)	0.977
Urinary protein (g/day)	−0.043	(0.122)	0.730
Creatinine clearance (mL/min/1.73 m^2)	0.006	(0.009)	0.501
Blood urea nitrogen (mg/dL)	−0.035	(0.032)	0.278
Creatinine (mg/dL)	0.031	(0.192)	0.874
Uric acid (mg/dL)	−0.096	(0.129)	0.463
Na (mEq/L)	0.004	(0.008)	0.609
K (mEq/L)	0.203	(0.234)	0.394
Total protein (g/L)	0.200	(0.281)	0.485
Albumin (g/L)	−0.011	(0.016)	0.490
Immunoglobulin G (mg/dL)	0.001	(0.000)	0.204
Immunoglobulin A (mg/dL)	0.001	(0.001)	0.584
Immunoglobulin M (mg/dL)	0.003	(0.002)	0.096
C3 (IU/mL)	0.001	(0.011)	0.943
C4 (IU/mL)	−0.024	(0.026)	0.378
CH50 (U/mL)	−0.002	(0.002)	0.494
eGFR (mL/min/1.73 m^2)	0.004	(0.007)	0.545

B sex- and age-adjusted regression coefficient with Log_{10}%GI-amyloid

renal disease are common in patients with RA, and therefore, this condition might also be the cause of proteinuria and haematuria [22–24].

There have been several attempts to establish an effective protocol for the treatment of reactive AA amyloidosis associated with RA, including use of corticosteroids, immunosuppressants and biologics such as TNF-α and IL-6 receptor antagonist to control RA disease activity and to improve kidney function and overall patient survival [31–33].

Gastrointestinal biopsy was recently established as a screening method of AA amyloidosis. However, the correlation between the degree of GI amyloidosis and clinical parameters had not yet been fully investigated. Now, our study shows a lack of correlation between the degree of GI amyloidosis and clinical parameters. All the GI amyloidosis-positive patients showed renal amyloidosis. This confirms the data we previously reported [13]. Additionally, this time, despite the degree of amyloid deposits being more evident in the gastric tissue than in renal tissue, we found them to be not statistically significant. Although no clinical parameters correlated with the amyloid-deposited area in gastric tissue, this was more than what is detected in renal tissue. GI biopsy was considered to be ideal for the screening of amyloidosis because of convenience and sensitivity. However, the timing of gastric biopsy must be considered with other aspects of amyloidosis, such as renal insufficiency, diarrhoea and malabsorption.

Some reports had suggested that patients with AA amyloidosis have laboratory signs of inflammatory process, with significantly increased plasma levels of acute-phase proteins, such as CRP [13, 34]. In our patients, there has been high disease activity in their clinical course of RA. Mild azotaemia and depression of Ccr were frequent, with which indicated renal insufficiency. Urinary abnormalities (proteinuria and haematuria) were also common in these patients.

These same conditions were observed in our amyloidosis patients.

In our experience, the severity of renal amyloidosis has been difficult to determine. Nevertheless, we considered the amyloidosis area occupied in renal tissue to be an important marker. We recently reported the effect of anti-TNF therapy for rapid removal and sustained disappearance of amyloid deposits in gastric mucosal tissue with amelioration of renal functions [31]. Thus, we speculated that rapid removal of amyloid deposits from renal tissue may have resulted in the amelioration of renal function. Yet the correlation between the amount of amyloidosis in GI tissues and clinical parameters including renal function was not clear. Serological indices, such as Cr, BUN, were not significantly correlated with Log_{10}%GI-amyloid. In the meantime, urinary protein was not correlated, despite most clinicians believing that urinary protein was an important marker of systemic amyloidosis. Additionally, we performed sex- and age-adjusted association between log_{10}%GI-amyloidosis and each clinical variable by multiple linear regression analysis. All the parameters including the level of Cr, BUN, Ccr and eGFR were not significantly correlated.

In conclusion, we found no significant correlation between amyloid-positive area in GI tissues and clinical parameters such as renal function, especially Cr, Ccr and eGFR. Urinary protein, considered as an important marker in renal amyloidosis, did not correlate with amyloid-positive area in GI specimen. Moreover, GI amyloid-positive areas were found to be larger than renal amyloid-positive areas. Therefore, the use of amyloid-deposited area in GI tissues was sufficient to use for the diagnosis of amyloidosis when compared with renal tissues for its convenience and sensitivity.

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

References

1. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S et al (2007) Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischemic heart disease and in pulmonary fibrosis. Rheumatology 46:350–357
2. Baecklund E, Lliadou A, Askling J, Ekbom A, Backlin C, Granath F et al (2006) Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 54:692–701
3. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE (2005) Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 52:722–732
4. Watson DJ, Rhodes T, Guess HA (2003) All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 30:1196–1202
5. Gertz MA, Kyle RA (1991) Secondary systemic amyloidosis: response and survival in 64 patients. Medicine (Baltimore) 70:246–256
6. Gillmore JD, Lovat L, Persey MR, Pepys MB, Hawkins PN (2001) Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid protein. Lancet 358:24–29
7. Husby G, Marhaug F, Dowton B, Sletten K, Sipe JD (1994) Serum amyloid A (SAA): biochemistry, genetics and the pathogenesis of AA amyloidosis. Amyloid 1:119–137
8. Cunnane G, Whitehead AS (1999) Amyloid precursors and amyloidosis in rheumatoid arthritis. Baillieres Clin Rheumatol 13:615–628
9. Kobayashi H, Tada S, Fuchigami T, Okuda Y, Takasugi K, Matsumoto T et al (1996) Secondary amyloidosis in patients with rheumatoid arthritis: diagnostic and prognostic value of gastroduodenal biopsy. Br J Rheumatol 35:44–49
10. El Mansoury TM, Hazenberg BP, El Badawy SA, Ahmed AH, Bijzet J, Limburg PC et al (2002) Screening for amyloid in subcutaneous fat tissue of Egyptian patients with rheumatoid arthritis: clinical and laboratory characteristics. Ann Rheum Dis 61:42–47
11. Wakhlu A, Krisnani N, Hissaria P, Aggarwal A, Misra R (2003) Prevalence of secondary amyloidosis in Asian North Indian patients with rheumatoid arthritis. J Rheumatol 30:948–951
12. Husby G (1985) Amyloidosis and rheumatoid arthritis. Clin Exp Rheumatol 3:173–180
13. Kuroda T, Tanabe N, Sakatsume M, Nozawa S, Mitsuka T, Ishikawa H et al (2002) Comparison of gastroduodenal, renal and abdominal fat biopsies for diagnosing amyloidosis in rheumatoid arthritis. Clin Rheumatol 21:123–128
14. Carmona L, Gonzalez-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmarti R (2003) Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis 62:897–900
15. Misra R, Wakhlu A, Krishnani N, Hissaria P, Aggarwal A (2004) Prevalence of silent amyloidosis in rheumatoid arthritis and its clinical significance. J Rheumatol 31:1031–1034
16. Tada S, Iida M, Iwashita A et al (1990) Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. Gastrointest Endosc 36:10–14
17. Ribera R (1971) Endoscopic diagnosis of amyloidosis. Gastrointest Endosc 17:137–144
18. Yamada M, Hatakeyama S, Tsukagoshi H (1985) Gastrointestinal amyloid deposition in AL (primary or myeloma associated) and AA (secondary) amyloidosis. Diagnostic value of gastric biopsy. Hum Pathol 16:1206–1211
19. Obana M, Adachi M, Matsuoka Y, Irimajiri S, Kishimoto H (1990) Amyloidosis in RA 127 Fukuda J. Clinical studies on amyloidosis complicated with rheumatoid arthritis–with particular reference to nephropathy. Jpn J Med 29:274–282
20. Samuels B, Lee JC, Engelman EP, Hooper J Jr (1978) Membranous nephropathy in patients with rheumatoid arthritis: relationship to gold therapy. Medicine 57:319–327
21. Hordon LD, Sellars L, Morley AR, Wilkson R, Thompson M, Griffiths AD (1984) Haematuria in rheumatoid arthritis: an association with mesangial glomerulonephritis. Ann Rheum Dis 43:440–443
22. Helin JH, Korpela MM, Mustonen TJ, Pasternack IA (1995) Renal biopsy findings and clinicopathologic correlations in rheumatoid arthritis. Arthritis Rheum 38:242–247
23. Nakano M, Ueno M, Nishi S, Shimada H, Hasegawa H, Watanabe T et al (1998) Analysis of renal pathology and drug history in 158 Japanese patients with RA. Clin Nephrol 50:154–160
24. Makino H, Yoshinaga Y, Yamasaki Y, Morita Y, Hashimoto H, Yamamura M (2002) Renal involvement in rheumatoid arthritis: analysis of renal biopsy specimens from 100 patients. Mod Rheumatol 12:148–154
25. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324
26. Imai E, Hiroe M, Nitta K, Yamagawa K, Iseki K, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Modification of the modification of diet in renal disease (MDRD) study equation for Japan. Am J Kidney Dis 50(6):927–937
27. Libbey CA, Skinner M, Cohen AS (1983) Use of abdominal fat tissue aspirate in the diagnosis of systemic amyloidosis. Arch Intern Med 143:1549–1552
28. Blum A, Sohar E (1962) The diagnosis of amyloidosis. Ancillary procedure. Lancet 1:721–724
29. Gafni J, Sohar E (1975) Rectal biopsy for the diagnosis of amyloidosis. Am J Med Sci 240:271–299
30. Fentem PH, Turnberg LA, Woemsley KG (1962) Biopsy of the rectum as an aid to diagnosis of amyloidosis. Br Med J 1:364–367
31. Kuroda T, Wada Y, Kobayashi D, Murakami S, Sakai T, Hirose S, Tanabe N, Saeki T, Nakano M, Narita I (2009) Effective anti-TNF-α therapy can induce rapid resolution and sustained decrease of gastroduodenal mucosal amyloid deposits in reactive amyloidosis associated with rheumatoid arthritis. J Rheumatol 36:2409–2415
32. Okuda Y, Takasugi K (2006) Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid. A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum 54(9):2997–3000
33. Nakamura T, Higashi S, Tomoda K, Tsukano M, Baba S (2007) Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. Clin Exp Rheumatol 25(4):518–522
34. Okuda Y, Takasugi K, Oyama T, Oyama H, Nanba S, Miyamoto T (1997) Intractable diarrhea associated with secondary amyloidosis in rheumatoid arthritis. Ann Rheum Dis 56:535–541