Epidemiological survey and risk factor analysis of dialysis-related amyloidosis including destructive spondyloarthropathy, dialysis amyloid arthropathy, and carpal tunnel syndrome

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Abstract

The purpose of this study was to investigate the incidence of dialysis-related amyloidosis (DRA) such as destructive spondyloarthropathy (DSA), dialysis amyloid arthropathy (DAA), and carpal tunnel syndrome (CTS). DAA was rated on X-ray images based on the disease stage. Of the 199 patients on regular dialysis therapy, 41 (20.6%) showed DRA. Based on the X-ray images, 21 patients (10.6%) showed DSA, while 22 patients (11.1%) showed DAA. Sixteen patients (8.0%) had CTS, determined through a history of surgery. Regarding overlap of conditions, 14 had both DSA and DAA, 3 had both DSA and CTS, and 2 had both DAA and CTS. A long duration of dialysis was a risk factor for DRA.

Key words: Regular dialysis therapy; Dialysis-related amyloidosis; Destructive spondyloarthropathy; Dialysis amyloid arthropathy; Carpal tunnel syndrome

Introduction

Epidemiological surveys of regular dialysis therapy (RDT) in Japan have been conducted annually by the Japanese Society for Dialysis Therapy since 1968. The RDT population, initially at 215 patients, exceeded 300,000 in 2011, with a total of 329,609 patients at the end of December 2016. During the one-year period in 2016, 39,344 patients were newly placed on dialysis, and 31,790 patients passed away, resulting in an increase of 7,544 patients(1). Moreover, with the increase in the number of RDT patients, cases of dialysis-related amyloidosis (DRA) are also increasing. In particular, the number of DRA patients treated surgically for destructive spondyloarthropathy (DSA) has been steadily increasing at our hospital. Past reports of epidemiological surveys of DRA-related vertebral joint lesions in RDT patients are rare. Moreover, to the best of our knowledge, there are no reports on a dialysis amyloid arthropathy (DAA) grading system similar to the one reported for DSA. We began the screening of dialysis patients in October 2009 and started our survey on DRA. The purpose of this study was to investigate the incidence of DRA, such as DSA, DAA, and carpal tunnel syndrome (CTS), in RDT patients and to report the grading for DAA.

Materials and Methods

The survey was conducted from October 2009 to September 2011 at main RDT institutions in the region that agreed to participate in the study. Of the approximately 240 RDT patients at the two institutions that agreed to cooperate in the survey, 199 who gave consent to participate in this study and underwent examinations were investigated. Patients on peritoneal dialysis were excluded. The survey was conducted in the patient's birth month, and data from the first year alone were used. Survey items included basic data such as sex, age, height, and weight and RDT-related factors such as kidney disease that led to RDT, age at start of RDT, RDT history, medical history (past and present), and history of surgery. DSA, DAA, and arteriosclerosis were diagnosed on the lateral X-ray view of the cervical spine, anteroposterior and lateral X-ray views of the lumbar spine, and anteroposterior X-ray views of the hip, both knees, and both hands.

DSA of the cervical and lumbar spine on lateral X-rays was classified from Grade 0 to Grade III in accordance with Chin et al.(2) Grade 0 does not show any abnormalities except spondylotic changes; Grade I shows bony erosion at the anterior vertebral rim; Grade II shows distinct bony erosion or radiolucent lesions in the vertebral endplates

within the narrowed intervertebral disc space; and Grade III shows the absence of intervertebral disc spaces. The grades and X-rays of representative cases are shown in Figure 1. In the present study, Grade 0 was defined as no DSA changes, and Grades I-III were defined as the presence of DSA.

Since there are no reports on the evaluation of DAA using anteroposterior X-rays of the hip, both knees, and both hands, a new grading system was established according to disease progression (Figures 2 and 3). Grade 0 shows no abnormalities except for age-related osteoarthritis; Grade I shows bone cysts (BCs) in the absence of joint destruction; Grade II shows destruction of the articular surface and joint space narrowing; and Grade III shows the absence of the joint space due to joint destruction. As for DSA, Grades I-III were defined as the presence of DAA.

For CTS, those who had undergone carpal tunnel release according to their medical history were included. In the present study, patients presenting any of the three (DSA, DAA, and CTS), alone or in combination, were considered to have DRA.

SPSS Ver.22 software was used for statistical analysis. Fisher's exact test or the Wilcoxon signed rank test was used for univariate analyses, and logistic regression was

used for multivariate analysis. Informed consent was obtained from all individual participants included in the study. This study was approved by the Ethics Committee of Nagasaki University (approval number: 09072467).

Results

There were 125 men and 74 women in this study. The mean age at the time of the survey was 64.6±12.6 (24-100) years, the age at the start of RDT was 54.7±16.3 (14-99) years, and the duration of RDT was 10.0±8.6 (1-43) years. Kidney diseases that resulted in RDT were chronic glomerulonephritis (36%), diabetic nephropathy (23%), nephrosclerosis (9%), IgA nephropathy (3%), polycystic kidney (2%), others (9%), and unknown (18%) (Figure 4). Treatment methods were hemodialysis (HD, n=197) and hemofiltration (n=2).

There were 42 patients with DRA, all of whom were on HD. Of these patients, 21 (10.6%) had DSA, 22 (11.1%) had DAA, and 16 (8.0%) had CTS. The sites and grades of the DRA, as well as the duration of RDT and age at the start of RDT, are shown in Table 1. Of the 21 patients with DSA, 19 (9.5%) had cervical DSA, and 10 (5.2%) had

lumbar DSA. Eight patients (3.8%) showed DSA at both cervical and lumbar spine levels. There were no patients with Grade III lumbar DSA. DAA (n=22) was present in the fingers (n=15; distal interphalangeal, n=6; proximal interphalangeal, n=12; metacarpophalangeal, n=2), wrist (n=9; carpals, n=2; distal end of the radius, n=1), hip joint (n=6), and knee (n=1). Except for the fingers, Grade III DAA was only observed in one patient at the hip (Case No. 23). The relationships among DSA, DAA, and CTS are shown in Figure 5. Fourteen patients had both DSA and DAA, three had both DSA and CTS, and two had both DAA and CTS. Univariate analysis showed that RDT history and age at start of RDT were associated with the presence/absence of DRA, and logistic regression analysis showed that a long history of RDT was a risk factor for DRA (Table 2).

Discussion

As previously described, the number of RDT patients in Japan is steadily rising, with an annual increase of 6,000 to 8,000 patients(1). An increase in the number of patients with chronic kidney disease (CKD) has also been reported from other countries.

Roderick et al (3) reported in a 2009 study from t4he UK that Stage 3 or greater CKD was seen in 6% of the population. The Singapore Renal Registry Annual Report 2015 (4) reported that the number of patients with CKD increased approximately 1.8-fold in 10 years since 2004. With the rising number of CDT patients, the number of patients treated for RDT-related complications is also increasing at our hospital.

The precursor protein of Aβ2M amyloid fibrils that causes DRA is β2 microglobulin, which is a component of MHC-class I antigen, produced by all nucleated cells and released into the extracellular fluid (5-7). However, it has been reported that the circulating concentration of β2M and the onset of DRA are not causally related (8). Rather, it is thought that misfolded (unnaturally folded) β2 microglobulin, which is present in a certain percentage of HD patients, turns into amyloid fibrils, thereby contributing to the onset of DRA (5-7,9).

Vertebral lesions that develop in RDT patients can be roughly divided into those that develop with amyloid as the primary cause and those that develop together with conditions such as calcification. The two distinct types of vertebral DRA are those that show bone destruction through amyloid deposition and those that form a mass.

Similarly to the DSA reported by Kuntz et al (10), a pathology primarily induced by bone destruction due to amyloid is well-known. However, there are other conditions such as vertebral amyloid deposition in which spinal canal stenosis is induced due to amyloid deposition. In addition, there is also an in-between condition of the above two types, called periodontoid lesion, where amyloid accumulates and a mass forms, inducing bone destruction. Lesions with calcification include yellow ligament calcification and peridural calcification. Moreover, the existence of many other disease states has been verified. Now the aforementioned vertebral lesions are all recognized as "dialysis-associated spondylosis."

The primary purpose of the current study was to investigate the incidence of DRA. DSA and DAA were found in 10.6% and 11.1% of the study population, respectively, on X-ray examination, and CTS occurred in 8.0% based on the medical history. The incidence of DSA based on X-ray findings was 18% according to a 1989 study by Fiocchi et al (11) and 19.4% according to a 2001 study by Leon et al (12). Moreover, in a 2005 report by Yamamoto et al (13), DSA was present in 123/612 (20.1%) patients, while DAA was present in 85 (13.9%) patients, with 20 patients having both DSA and

DAA. Compared to previous reports, the present study showed a lower incidence, and we postulated that this was because the present study included patients who had a short RDT history (mean, ~10 years), and the recent improvement in RDT made a great contribution, since the present study was conducted more recently than past studies. On this point, Hoshino et al (14) also reported in 2016 that the onset risk of CTS and DAA, which are characteristic clinical symptoms of DRA, has been decreasing in recent years.

It has been previously noted that destruction of the finger is commonly observed in DSA patients. In the present study, there was a high incidence of DAA of the finger (12/22 patients, 54.5%). On X-ray examination of DAA, bone destruction starts from the BC at the ligament attachment site, gradually spreading to the articular surface. The findings are completely divergent from Heberden nodes, where the narrowing of the articular space is observed first. For this reason, Heberden nodes were excluded in this study. There are no unified terms in past reports regarding destruction of the finger, and various terms such as arthritis (15), erosive arthropathy (16), erosive osteoarthritis (17), erosive azotemic osteoarthropathy (18), and erosive azotemic osteodystrophy (19) have been used. We label Grade II and III conditions “destructive arthropathy of the finger,”

named after DSA, since the destructive lesion is the major symptom. The bone destruction seen in DSA and DAA may be the same pathological condition. However, even though the present study included the hip, knee, and wrist, as well as the finger, clear destruction of the articular surface was rare in sites other than the finger, except for only one patient with such destruction at the hip, although narrowing of the articular space due to BC and osteoarthritis was observed. We postulated that DAA caused by HD likely occurs at small joints such as the vertebrae and fingers, rather than in large joints, or that changes in large-joint DAA may be difficult to ascertain with X-ray examinations alone.

As a risk factor for DRA, similar to the present survey results, long-term dialysis has been suggested (14,20). Specifically, Koch reported that the onset of DRA cannot be avoided in patients with a dialysis history of 20 years or longer (20). Moreover, it has been shown that 100% of patients who started HD at 30 years old or older developed CTS (21), and that starting HD at an older age is a risk factor for DSA (22,23). However, these trends for DRA overall were not seen in the present survey.

The limitations of this study were as follows: only X-ray examinations were used to diagnose DSA and DAA, and, thus, detailed evaluations with computed tomography (CT) or magnetic resonance imaging (MRI) were not conducted; CTS was not directly examined; and the design was cross-sectional rather than longitudinal. We occasionally see patients who do not show vertebral abnormalities on X-rays, but show bone destruction on CT or MRI. Moreover, when the intervertebral joint alone is destroyed, it is difficult to diagnose with X-ray images alone. Our goal is therefore to be able to conduct a true assessment of incidence using CT or MRI in the future; however, this is extremely expensive and not realistic at the present time for screening.

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Figure Legends

Fig. 1. DSA　Grading

A: Grade 0 did not show any abnormalities except some spondylotic changes, B: Grade I showed bony erosion at the anterior vertebral rim, C: Grade II showed distinct bony erosion or radiolucent lesions in the vertebral endplates along with narrowed intervertebral disc space, D: Grade III showed absence of the intervertebral disc space, and Grades Ⅰ, II and III were defined as DSA.

Fig. 2. DAA Grading (Finger)

A: Grade 0 did not show any abnormalities except some osteoarthritis changes, B: Grade I showed Bone erosion in ligament attachment area, C: Grade II showed distinct bony erosion or radiolucent lesions in the subchondral bone along with narrowed joint space, D: Grade III showed absence of the joint space with Joint destruction,

Fig. 3. DAA on XP.

A bone cyst in Lunate, scaphoid and distal radius as Grade I, B. bone cyst in distal femur as Grade I, C. bone cyst in femoral head as Grade I, D. absence of the Hip joint space with Joint destruction as Grade III

Fig. 4. The Proportion of diseases that caused HD.

Chronic glomerulonephritis was the most common. It also exceeded half in total with chronic glomerulonephritis and diabetic nephropathy.

Fig.5. DRA: The relationships among DSA, DAA and CTS

Table 1. Details of 41 DRA cases

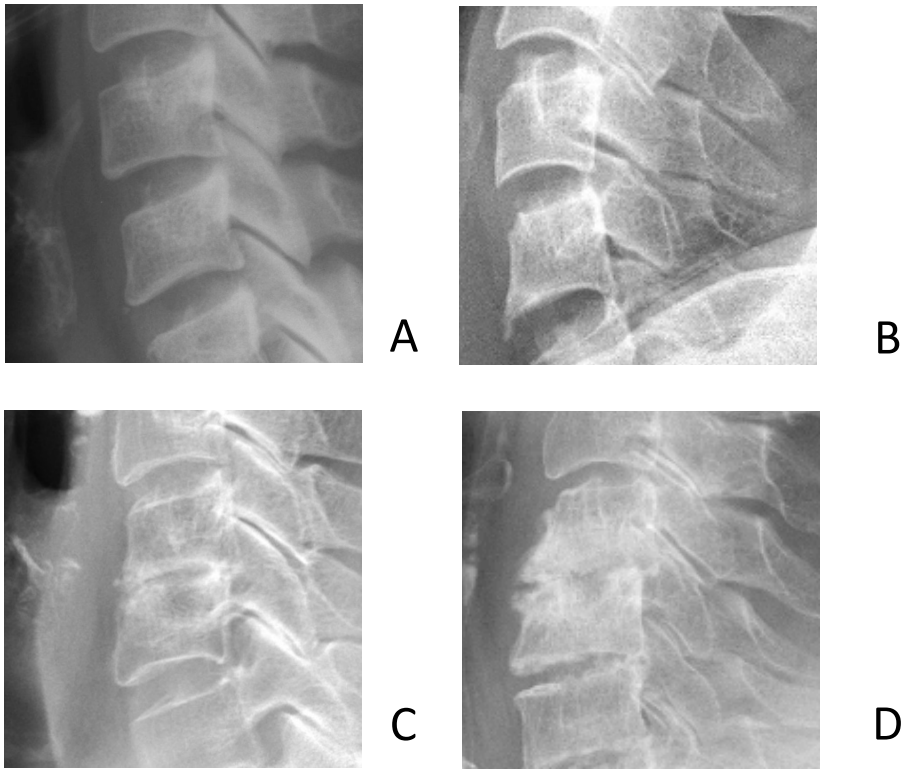
Of the 21 patients with DSA, 19 (9.5%) had cervical DSA, and 10 (5.2%) had lumbar DSA. Eight patients (3.8%) showed DSA at both cervical and lumbar spine levels. DAA (n=22) was present in the fingers (n=15; distal interphalangeal, n=6; proximal interphalangeal, n=12; metacarpophalangeal, n=2), wrist (n=9; carpals, n=2; distal end of the radius, n=1), hip joint (n=6), and knee (n=1). Except for the fingers, Grade III

DAA was only observed in one patient at the hip (Case No. 23).

Chronic glomerulonephritis (CGN), Diabetic Nephropathy (DMN or DN), nephrosclerosis , chronic tubulointerstitial nephritis(CTIN), Nephrotic syndrome(NS), purpura nephritis (PN), Polycystic Kidney(PK)

Table 2. Univariate analysis and Multivariate logistic regression analysis of DRA

Univariate analysis showed that RDT history and age at start of RDT were associated with the presence/absence of DRA, and logistic regression analysis showed that a long history of RDT was a risk factor for DRA .



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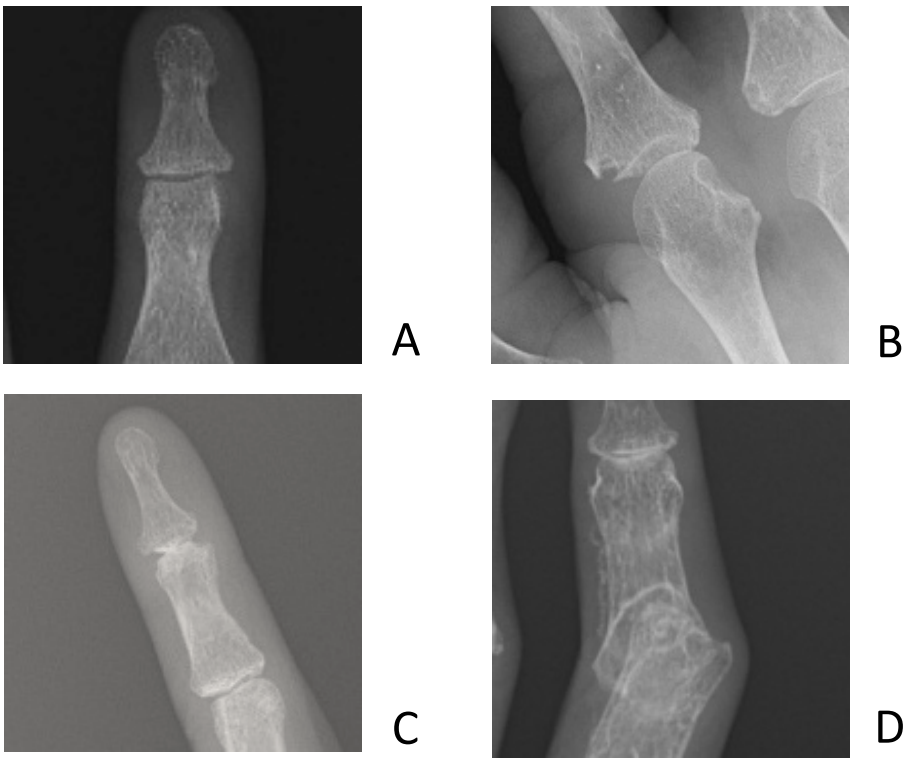

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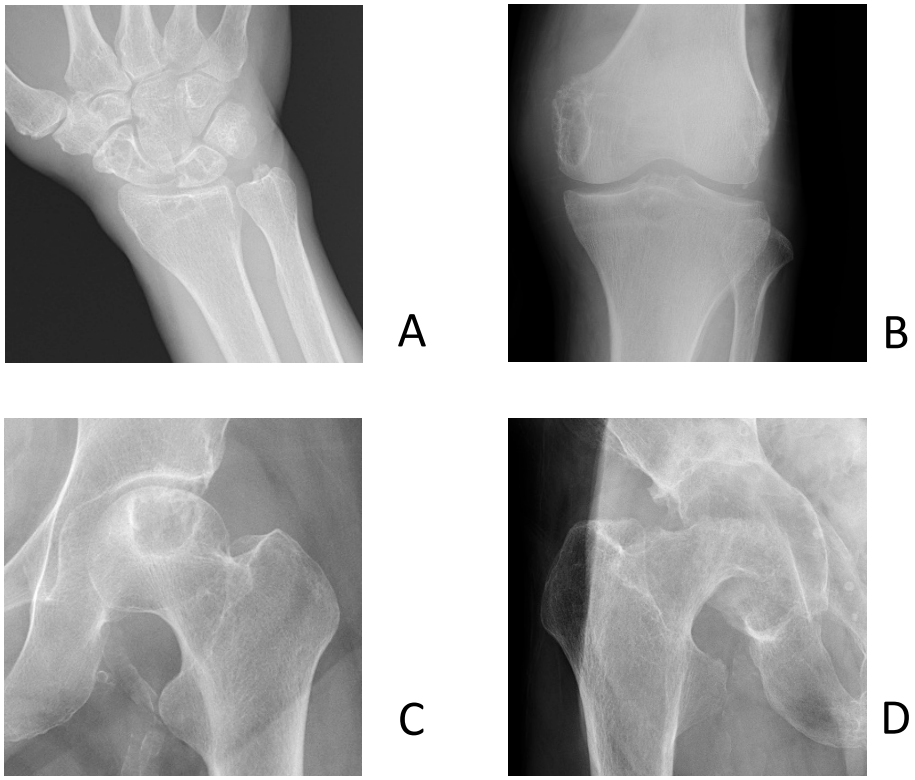

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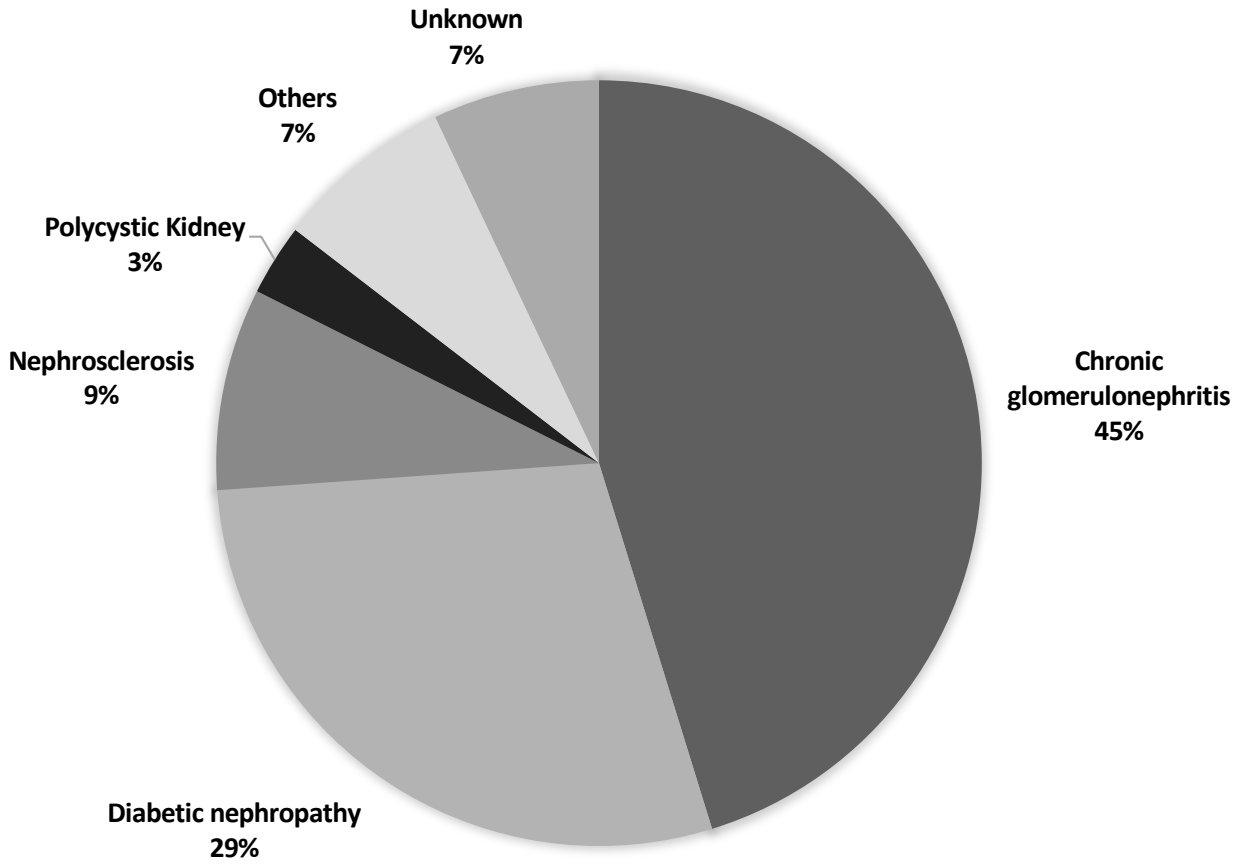

Fig. 4. The Proportion of diseases that caused CDT.

Chronic glomerulonephritis was the most common. It also exceeded half in total with chronic glomerulonephritis and diabetic nephropathy.

Case No.	age	gender	Period of CDT	Age at initial CDT	Cause*	DSA level (Grade)**	DAA joint (Grade)	CTS
1	50	female	27	23	CGN	C (II)	Hip (I)	+
2	67	male	36	31	CGN	C(II)	Hip (I), knee (I)	-
3	53	male	27	26	CGN	C (I) L (I)	wrist (I)	-
4	46	male	26	20	CGN	C (II)	wrist (I)	-
5	55	female	22	33	CTIN	C(II), L (II)	finger (III)	-
6	71	female	21	50	CGN	C(II, III) L(II)	finger (II), wrist (I)	-
7	70	male	21	49	NS	C (II)、L (II)	wrist (I)	-
8	76	male	20	56	CGN	C(III)	wrist (I)	-
9	76	female	18	58	CGN	C(I)	finger (II)	-
10	74	female	17	57	CGN	(II)	finger (II)	-
11	57	female	13	44	CGN	C (I)、L(I)	finger (III)	-
12	71	male	12	59	PK	C(II)、L(II)	finger (II)	-
13	45	female	4	41	DMN	C (II)	finger (I), Hip(I)	-
14	67	female	1	66	DMN	C(I), L (I)	finger (I)	-
15	65	male	24	41	CGN	C (III)	-	+
16	59	male	17	42	unknown	C(II)	-	+
17	57	male	25	32	CGN	C (II)	-	-
18	64	male	19	45	DMN	C(II)	-	-
19	52	male	15	37	CGN	C(II), (II)	-	-
20	51	female	5	46	nephrosclerosis	L(II)	-	-
21	61	male	1	60	DMN	L(II)	-	-
22	76	male	22	54	nephrosclerosis	-	finger (I), wrist (I)	+
23	62	male	32	30	CGN	-	finger (I), wrist (I), hip (III)	-
24	80	male	16	64	CGN	-	wrist (I)	-
25	76	female	14	62	CGN	-	wrist (I)	-
26	84	female	12	72	unknown	-	finger (I)	-
27	87	male	6	81	CGN	-	finger (I), Hip (I)	-
28	63	female	4	59	DMN	-	finger (I), Hip (I)	-
29	59	male	4	55	DMN	-	finger (I), Hip (I)	-
30	57	female	27	30	PN	-	-	+
31	59	male	27	32	CGN	-	-	+
32	61	female	26	35	SLE	-	-	+
33	47	female	26	21	CGN	-	-	+
34	69	female	25	44	CGN	-	-	+
35	74	male	24	50	CGN	-	-	+
36	68	male	23	45	CGN	-	-	+
37	59	female	21	38	CGN	-	-	+
38	46	male	20	26	CGN	-	-	+
39	66	male	12	54	CGN	-	-	+
40	74	male	10	64	CGN	-	-	+
41	62	male	1	61	DMN	-	-	+

Table 1. Details of 41 DRA cases

Cause*: Chronic glomerulonephritis (CGN), Diabetic Nephropathy (DMN or DN), nephrosclerosis , chronic tubulointerstitial nephritis(CTIN)、Nephrotic syndrome(NS), purpura nephritis (PN), Polycystic Kidney(PK)

DSA level**: C(Cervical Spine), L(Lumber Spine)

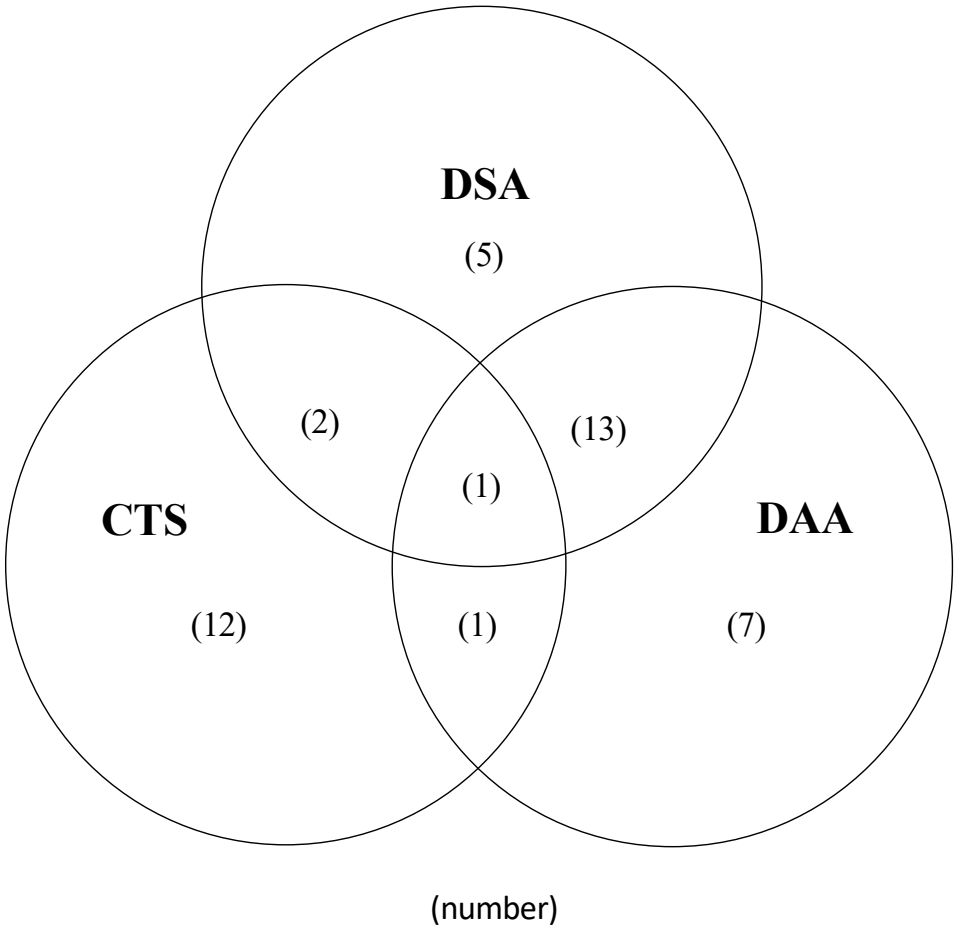

Fig.5. DRA: The relationships among DSA, DAA and CTS

grade	n	Age at the start of RDT	Period of RDT	age
0	178	60.0±16.2	9.1±8.1	65.0±12.9
Ⅰ	5	45.0±17.1	19.0±13.4	64.0±9.1
Ⅱ	13	41.8±12.8	16.2±8.6	58.1±9.5
Ⅲ	3	49.0±7.5	21.7±2.1	70.6±5.5

Table 2. Age at the start of RDT, period of RDT and age of each DSA grade

grade	n	Age at the start of RDT	Period of RDT	age
0	177	55.2±16.2	9.1±8.1	64.4±12.7
Ⅰ	12	51.1±19.9	15.0±9.6	66.1±15.1
Ⅱ	7	52.9±10.1	18.3±9.7	71.1±4.8
Ⅲ	3	35.7±7.4	22.3±9.5	58.0±3.6

＊average ± Standard Deviation

Table 3. Age at the start of RDT, period of RDT and age of each DAA grade

	Univariate analysis of DRA			Multivariate logistic regression analysis of DRA		
	DRA	Non DRA	p value	*p* value	Odd ratio	95%CI
number	41	158				
Men : women	24:17	15:26	0.5875			
Chronic glomerulonephritis＊	26:15	65:93	0.0136	0.9767	1.0159	0.351-2.932
Diabetic Nephropathy＊	7:34	50:108	0.0812	0.5659	1.473	0.391-5.544
PS membrane＊	37:4	129:29	0.2418			
CTA membrane＊	2:39	9:149	0.7031			
Age at the start of RDT	46.2 ± 14.9 (45)	56.9 ± 16.0 (58)	0.0002	0.2868	1.020	0.980-1.060
period of RDT	17.6 ± 9.1 (20)	8.0 ± 7.4 (6)	0.0001	0.0001	514.183	18.982-17344.340
age	63.8 ± 10.7 (63)	64.8 ± 13.1 (64.5)	0.5108			
height	157.1 ± 10.2 (157.5)	158.2 ± 57.4 (157.7)	0.4148			
body weight	52.9 ± 10.5 (51)	57.4 ± 11.8 (55.6)	0.0253	0.8056	0.997	0.954-1.041
WBC($x10^3/\mu l$)	4960 ± 2457 (4300)	5155 ± 1781 (5100)	0.1180			
RBC($x10^3/\mu l$)	340 ± 56 (337)	345 ± 45 (344)	0.1513			
Hb(g/dl)	11.5 ± 5.3 (10.8)	10.7 ± 1.0 (10.8)	0.9934			
Hct(%)	32.1 ± 3.2 (32.5)	32.3 ± 3.3 (32.5)	0.6748			
PLT($x10^3/\mu l$)	17.80 ± 11.36 (15.45)	27 ± 37.41 (18.55)	0.0361	0.0936	0.985	0.960-1.011
β2M(μg/ml)	27.3 ± 6.0 (27.4)	26.9 ± 6.6 (26.6)	0.8394			
Ca(mg/dl)	9.0 ± 0.9 (9.5)	8.7 ± 0.9 (8.7)	0.0798	0.1664	1.375	0.855-2.211
P(mg/dl)	5.3 ± 1.1 (5.3)	5.1 ± 1.4 (5.1)	0.5688			
ALP(U/L)	280 ± 114 (258)	269 ± 160 (232)	0.1916			
BALP(U/L)	17.0 ± 6.1 (16.3)	16.8 ± 11.6 (13.9)	0.1313			
CRP(mg/dl)	0.65 ± 1.31 (0.19)	0.53 ± 1.20 (0.15)	0.3666			
Intact PTH(pg/dl)	186.0 ± 86.0 (179.5)	182.2 ± 141 (150.0)	0.195			

＊(with : without)
average ± Standard Deviation (Median)

Table 4. Univariate analysis and Multivariate logistic regression analysis of DRA