



# ANCA-associated nephritis without crescent formation has atypical clinicopathological features: a multicenter retrospective study

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## Abstract

**Background** Although crescentic glomerulonephritis is a hallmark of ANCA-associated nephritis, the clinicopathological features of ANCA-associated nephritis without crescent formation remain to be elucidated.

**Methods** We enrolled 146 Japanese ANCA-associated vasculitis (AAV) patients subjected to renal biopsy in 16 hospitals from 2001 to 2018, and compared those with and without crescent formation (C+ and C− groups). The primary endpoint was end-stage renal disease (ESRD) and/or death.

**Results** C− group comprised 25 (17.1%) subjects. They had better renal function at the time of renal biopsy [estimated glomerular filtration rate (eGFR); median 41.7 vs 27.5 ml/min/1.73 m<sup>2</sup>,  $p < 0.01$ ] with minor urinary abnormalities but had a higher serum C-reactive protein level (8.8 vs 5.4 mg/dl,  $p = 0.01$ ) and frequency of extra-renal lesions of AAV (76.0% vs 48.8%,  $p = 0.02$ ) than C+ group. Pathologically, C− group had a higher frequency of arteritis (40.0% vs 16.5%,  $p < 0.01$ ). Kaplan–Meier method with log-rank tests showed no significant difference in renal and life prognosis combined, regardless of crescent formation. Multivariate Cox regression analysis revealed baseline eGFR, sclerotic class, and extra-renal lesions to be risk factors of ESRD and death combined. Competing risk analysis showed baseline eGFR and sclerotic class to be associated with ESRD, whereas baseline eGFR and extra-renal lesions were associated with death.

**Conclusion** ANCA-associated nephritis without crescent formation had different clinicopathological features from those with crescent formation, suggesting an atypical subtype of ANCA-associated nephritis. Despite the better renal function at the time of renal biopsy, these results suggest that this subtype requires especially careful attention, especially in the presence of extra-renal involvement.

**Keywords** ANCA-associated nephritis · Crescent · Arteritis · Vasculitis

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## Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis predominantly affecting small vessels [1]. AAV is composed of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and single-organ AAV including renal-limited one [1]. The kidney is one of the major target organs of AAV [2], and the presence of renal lesions is one of the prognostic factors affecting survival in AAV [3].

Although crescentic glomerulonephritis is a hallmark of ANCA-associated nephritis, other microscopic renal lesions have also been reported. In renal vessels other than glomeruli, arteritis, arteriolitis, medullary angiitis, peritubular capillaritis, and venulitis can develop [4, 5].

Interlobular arteries are the most commonly affected small vessels. In tubules, acute or chronic lesions can develop, including tubulitis, and simplification or atrophy of tubular epithelial cells [4]. In interstitium, inflammation can develop around glomeruli induced by glomerular lesions, or around vessels by vasculitis [4]. Some cases have been reported to have interstitial inflammation independent of glomerular lesions [6, 7], suggesting peritubular capillaritis to be one of the causes of the tubulointerstitial nephritis of AAV [7]. Some cases develop these extra-glomerular lesions accompanied with crescentic glomerulonephritis, while others do not. The latter suggest that some ANCA-associated nephritis predominantly affects parts of kidneys other than glomerular capillaries.

Patients without crescent formation have been reported to account for 12–21% of AAV patients with renal disease [2, 8]. However, the clinicopathological features of ANCA-associated nephritis without crescent formation remain to be elucidated. This prompted us to undertake a multicenter retrospective cohort study in which ANCA-associated nephritis in cases with and without crescent formation was compared to better clarify the features and prognosis of ANCA-associated nephritis without crescent formation.

## Methods

### Patients

We enrolled 146 Japanese AAV patients subjected to renal biopsy in 16 hospitals from 2001 to 2018. We included AAV patients who fulfilled the Chapel Hill diagnostic criteria of AAV, regardless of positivity of MPO-ANCA or PR3-ANCA [1]. Secondary crescentic glomerulonephritis was excluded. Patients were classified as having MPA, GPA, or EGPA by the European Medicines Agency algorithm [9]. Patients with vasculitis only in kidneys were classified as having renal-limited AAV. The indication for kidney biopsy was urinary abnormalities, such as proteinuria or hematuria, and/or kidney dysfunction. We defined extra-renal lesions as ones which satisfied at least one of the following: (1) lesions of lung, joint, skin, nerve, muscle, or ear, in which histological proof of vasculitis and/or granuloma formation was detected; (2) specific investigations strongly suggestive of vasculitis and/or granuloma formation, i.e., lung (radiological abnormalities including interstitial lung disease and nodular lesions), joint (arthritis), skin (purpura, infarct, and ulcer), nerve (mononeuritis multiplex), muscle (myalgia), or ear (otitis media). Patients were treated based on the clinical judgement of the rheumatologist and nephrologist, and treatment guidelines and recommendations for AAV or rapidly progressive glomerulonephritis [10, 11].

### Clinical data

We measured clinical findings at the time of renal biopsy, including creatinine (Cr), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), total protein (TP), immunoglobulin (Ig) G, IgA, IgM, myeloperoxidase (MPO)-ANCA, and proteinase (PR) 3-ANCA in the serum, urinalysis, presence of comorbidities (hypertension, hyperlipidemia, diabetes mellitus, and hyperuricemia), and extra-renal lesions by AAV.

We also measured serum Cr and eGFR levels at the last patient visit, and recorded medications prescribed for AAV during the observation period. Renal function of end-stage renal disease (ESRD) patients was recorded just prior to starting dialysis or renal transplantation. eGFR was calculated from serum Cr using the formula of the Japanese Society of Nephrology [12]. ESRD was defined as the need for dialysis or renal transplantation.

### Renal pathology

Biopsy specimens were evaluated by three experienced nephropathologists for light microscopy, including hematoxylin and eosin, periodic acid Schiff, Masson trichrome, and periodic acid methenamine silver staining. If the opinions of any of the three nephropathologists differed, consensus was attained by face-to-face discussion. Glomerular lesions were expressed as the rate of involvement of all observed glomeruli. The definition of crescents followed that outlined in the previous report, including both cellular and fibrous ones [13]. The definition of global glomerulosclerosis also followed that in the previous report, including all global glomerulosclerosis regardless of attribution [13]. Arteritis and arteriolitis were defined as fibrinoid necrosis (red on hematoxylin and eosin and/or Masson trichrome staining) and infiltration of leukocytes in interlobular arteries and arterioles, respectively. The frequency of arteritis showed both the rate of all patients and that of patients with small arteries in their biopsy samples. Tubular atrophy and interstitial fibrosis were shown as the score of cortex observed (0, absent; 1, < 25%; 2, 25–50%; and 3, > 50% of the cortical area).

### Statistics

We compared clinical and pathological findings between those with and without crescent formation (C+ and C– groups). The primary endpoint was a combination of ESRD and death. Statistical calculations were performed by the SPSS software (version 24.0). Statistical analysis was performed using Mann–Whitney's *U*-test for continuous variables, and the  $\chi^2$  test or Fisher's exact test for

categorical variables as appropriate. For the time-to-event analysis, we considered that the follow-up of the patients started at the time of renal biopsy and came to an end at the time of the end of the observation period, death, or ESRD being reached. Cumulative event rates were analyzed using the Kaplan–Meier method with log-rank tests to compare between C+ and C– groups. Stepwise multivariate Cox regression analysis was performed with variables which were different in univariate comparison between C+ and C– groups ( $p < 0.1$ ). Then we performed confirmatory multivariate Cox regression analysis to compare these two groups, adjusted with two well-known prognostic factors on renal or life outcome in ANCA-associated nephritis, eGFR and sclerotic class, as well as variables detected to affect the outcome significantly by the previous analysis. Continuous variables (age, eGFR, protein excretion per day, and CRP) were normalized by Box–Cox transformation. Competing analysis was also performed using the same variables. Lastly, we repeated the same analysis with baseline eGFR-matched patients by propensity score-matching method. Data are shown as a median [interquartile range (IQR): 25th–75th percentiles].  $p < 0.05$  was considered as significant. Hazard ratio (HR) is expressed with 95% confidence intervals (CI). All statistical calculations were performed by the SPSS software (version 24.0).

The study was conducted according to all the provisions of the Declaration of Helsinki, and reviewed and approved by the local ethics committee.

## Results

Of 146 patients, C– group included 25 (17.1%). In clinical findings, there were no differences in age or sex between C– and C+ groups, but C– group had a higher frequency of diabetes mellitus (Table 1). C– group had better renal function [eGFR; 41.7 (IQR 36.0–75.0) vs 27.5 (IQR 13.0–45.0) ml/min/1.73 m<sup>2</sup>,  $p < 0.01$ ] and less proteinuria [0.5 (IQR 0.2–0.8) vs 1.0 (IQR 0.5–2.0) g/gCr,  $p < 0.01$ ] or hematuria (84.0% vs 95.9%,  $p = 0.05$ ) than C+ group. On the other hand, C– group had a higher CRP level than C+ group [8.8 (IQR 6.2–14.3) vs 5.4 (IQR 0.7–11.6) mg/dl,  $p = 0.01$ ]. Although there were no differences in any other clinical findings including ANCA serology, C– group had a higher frequency of extra-renal lesions of AAV than C+ group (76.0% vs 48.8%,  $p = 0.02$ ). Although the most frequent extra-renal lesion was in the lung in both groups without significant difference, C– group had higher frequencies of otitis media and myopathy (16.0% vs 3.3%, 20.0% vs 1.7%,  $p = 0.03$ ,  $< 0.01$ , respectively) than C+ group. In terms of composition of AAV, C– group had a significantly lower frequency of renal-limited AAV (16.0% vs 47.1%,  $p < 0.01$ ) and tended to have a higher frequency of GPA without significance (16.0% vs 4.1%,  $p = 0.05$ ). Frequencies of MPA

and EGPA were similar (68.0% vs 47.1% and 0% vs 1.7%,  $p = 0.08$  and 1.00, respectively).

In the histological findings, although C– group had fewer glomeruli [13 (IQR 12–25) vs 20 (IQR 15–30),  $p = 0.03$ ], patients with fewer than 10 glomeruli, the minimum number needed to make the diagnosis [13, 14], were fewer than 10% in both groups without significant difference (8.0% vs 7.4%,  $p = 1.00$ ). There were no differences in global glomerulosclerosis [15.4% (IQR 0–30.8) vs 12.3% (IQR 3.5–28.6),  $p = 0.86$ ], or the rate of patients with small arteries in the samples (64.0% vs 68.6%,  $p = 0.65$ ). Notably, C– group had a higher frequency of arteritis than C+ group. Similar results were obtained regarding both the rate of all patients (40.0% vs 16.5%,  $p < 0.01$ ) and the rate of patients with small arteries in their biopsy samples (62.5% vs 24.1%,  $p < 0.01$ ). C– group had less tuft necrosis [0% (IQR 0–0) vs 0% (IQR 0–9.1),  $p = 0.01$ ]. The scores of tubular atrophy and interstitial fibrosis were similar. In the glomerular histological classification, C– group had a higher frequency of focal class (88.0% vs 37.2%,  $p < 0.01$ ), and no crescentic or mixed classes, though sclerotic class did not differ between them (Table 2).

In the follow-up, 123 patients (84.2%) were tracked with sufficient clinical information for the purposes of this study as mentioned in “Methods” section. Although the rate of tracked patients was higher in C– group (100% vs 81.0%,  $p = 0.01$ ), the comparison of the tracked 123 patients between C– and C+ ones showed similar results to those of the overall 146 patients in Tables 1 and 2, especially in terms of renal function at the time of renal biopsy, comorbidities, sclerotic glomeruli, tubulointerstitial damage, sclerotic class, and focal class (data not shown).

As for treatment, C– group had less prednisolone (PSL) use (84% vs 97.0%,  $p = 0.03$ ). Frequency of use of other immunosuppressants, including cyclophosphamide, azathioprine, and mizoribine, was similar. Rituximab and plasma exchange were less used in both groups (Table 3).

The observation period did not differ between these groups [26.0 (IQR 9.0–67.0) vs 23.0 (IQR 5.0–62.5) months,  $p = 0.47$ ] (Table 4). Although C– group had better renal function at the last visit [eGFR; 47.4 (IQR 35.0–62.5) vs 34.6 (IQR 21.4–51.5) ml/min/1.73 m<sup>2</sup>,  $p = 0.03$ ], there were no differences in the rates of ESRD and/or death cases. In survival analysis, no significant difference was shown in cumulative event rates of ESRD and/or death (Fig. 1). The rate of change of eGFR from the time of renal biopsy to the last visit was lower in C– group [+5.6 (IQR – 18.6~ +22.3) % vs +18.9 (IQR – 81.2~ +94.2) %,  $p = 0.07$ ].

In order to detect factors associated with renal and life prognoses, we performed stepwise multivariate Cox regression analysis. As correlations (Pearson’s  $r > 0.7$ ) were detected among extra-renal lesions, renal-limited AAV, and MPA, we selected extra-renal lesions from them as a

**Table 1** Patient characteristics between C– and C+ groups at the time of renal biopsy

	C– (n=25)	C+ (n=121)	p
Age, years old (IQR)	74 (70–79)	70 (64–76)	0.14
Female, n (%)	14 (56.0)	62 (51.2)	0.83
Hypertension, n (%)	12 (48.0)	60 (49.6)	1
Hyperlipidemia, n (%)	8 (32.0)	26 (21.5)	0.30
Diabetes mellitus, n (%)	8 (32.0)	13 (10.7)	0.01
Hyperuricemia, n (%)	3 (12.0)	32 (26.4)	0.20
Cr, mg/dl (IQR)	1.1 (0.6–1.4)	1.7 (1.2–3.6)	<0.01
eGFR, ml/min/1.73 m <sup>2</sup> (IQR)	41.7 (36.0–75.0)	27.5 (13.0–45.0)	<0.01
Proteinuria, g/gCr (IQR)	0.5 (0.2–0.8)	1.0 (0.5–2.0)	<0.01
Hematuria, n (%)	21 (84.0)	116 (95.9)	0.05
CRP, mg/dl (IQR)	8.8 (6.2–14.3)	5.4 (0.7–11.6)	0.01
Total protein, g/dl (IQR)	6.7 (5.8–7.0)	6.6 (5.9–7.0)	0.88
IgG, mg/dl (IQR)	1459 (1347–1716)	1600 (1212–1952)	0.80
IgA, mg/dl (IQR)	322 (246–361)	285 (209–395)	0.61
IgM, mg/dl (IQR)	73 (52–170)	81 (58–120)	0.75
MPO-ANCA +, n (%)*	20 (87.0)	89 (89.9)	0.71
MPO-ANCA, IU/ml (IQR)*	119 (69–274)	148 (59–300)	0.72
PR3-ANCA +, n (%)*	5 (21.7)	11 (11.1)	0.18
PR3-ANCA, IU/ml (IQR)*	0 (0–8.0)	0 (0–0)	0.61
Extra-renal organ involvement			
Any organs, n (%)	19 (76.0)	59 (48.8)	0.02
Lung, n (%)	9 (36.0)	40 (33.1)	0.82
Joint, n (%)	1 (4.0)	9 (7.4)	1.0
Skin, n (%)	3 (12.0)	6 (5.0)	0.18
Nerve, n (%)	4 (16.0)	6 (5.0)	0.07
Muscle, n (%)	5 (20.0)	2 (1.7)	<0.01
Otitis media, n (%)	4 (16.0)	4 (3.3)	0.03
Composition of AAV			
MPA, n (%)	17 (68.0)	57 (47.1)	0.08
GPA, n (%)	4 (16.0)	5 (4.1)	0.05
EGPA, n (%)	0 (0)	2 (1.7)	1.0
Renal-limited AAV, n (%)	4 (16.0)	57 (47.1)	<0.01

Cr creatinine, eGFR estimated glomerular filtration rate, CRP C-reactive protein, MPO myeloperoxidase, ANCA antineutrophil cytoplasmic antibody, PR3 proteinase 3, MPA microscopic polyangiitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, AAV anti-neutrophil cytoplasmic antibody-associated vasculitis, IQR interquartile range

\*There are some missing data

variable. In all tracked patients, baseline eGFR, CRP, and sclerotic class were associated with ESRD and death combined [HR 0.694 (0.551–0.876), HR 1.530 (1.078–2.173), and HR 11.651 (2.988–45.435), respectively]. Competing risk analysis showed that ESRD was associated significantly with eGFR and sclerotic class [HR 0.367 (0.204–0.663) and HR 5.872 (1.334–25.845), respectively], whereas death was associated with eGFR and extra-renal lesions [HR 0.708 (0.545–0.920) and HR 7.783 (1.588–38.146), respectively].

To compare the differences in renal and life outcomes between C– and C+ groups, a confirmatory Cox regression analysis, adjusted for the above-mentioned variables (baseline eGFR, sclerotic class, and extra-renal lesion in Model 1;

baseline eGFR, sclerotic class, extra-renal lesion, and CRP in Model 2), was performed. Continuous variables (eGFR and CRP) were normalized by Box-Cox transformation ( $\lambda=0.5$ ). In all tracked patients (Table 5), ESRD and death combined were associated with baseline eGFR and extra-renal lesions in Model 1 [HR 0.661 (0.541–0.809) and HR 3.689 (1.645–8.274), respectively], and with baseline eGFR, sclerotic class, and extra-renal lesions in Model 2 [HR 0.671 (0.538–0.838), HR 3.622 (1.084–12.102), and HR 3.704 (1.344–10.211), respectively]. Competing risk analysis showed that ESRD was associated with baseline eGFR and sclerotic class in Model 1 [HR 0.488 (0.333–0.713) and HR 4.165 (1.289–13.454), respectively], and baseline eGFR

**Table 2** Histological findings between C– and C+ groups

	C– (n=25)	C+ (n=121)	p
Glomeruli, n (IQR)	13 (12–25)	20 (15–30)	0.03
Global sclerosis, % (IQR)	15.4 (0–30.8)	12.3 (3.5–28.6)	0.86
Crescent, % (IQR)	0 (0–0)	33.3 (19.0–54.5)	<0.01
Tuft necrosis, % (IQR)	0 (0–0)	0 (0–9.1)	0.01
Small arteries, n (%)	16 (64.0)	83 (68.6)	0.65
Arteritis, n (%)*	10 (40.0)	20 (16.5)	<0.01
Arteritis, n (%)**	10 (62.5)	20 (24.1)	<0.01
Arteriolitis, n (%)	5 (21.7)	14 (12.7)	0.32
PTCitis, n (%)	8 (32.0)	30 (24.8)	0.46
TA score (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.56
IF score (IQR)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	0.73
Sclerotic class, n (%)	3 (12.0)	14 (11.6)	1.0
Focal class, n (%)	22 (88.0)	45 (37.2)	<0.01
Crescentic class, n (%)	0 (0)	40 (33.1)	<0.01
Mixed class, n (%)	0 (0)	22 (18.2)	0.02

PTCitis peritubular capillaritis, TA tubular atrophy, IF interstitial fibrosis, IQR interquartile range

\*The rate of all patients, \*\*the rate of patients with small arteries in the samples

**Table 3** Medications for ANCA associated vasculitis between C– and C+ groups

	C– (n=25)	C+ (n=98)	p
PSL, n (%)	21 (84.0)	95 (96.9)	0.03
Cyclophosphamide, n (%)	3 (12.0)	17 (17.3)	0.76
Azathioprine, n (%)	2 (8.0)	8 (8.2)	0.68
Rituximab, n (%)	0 (0)	1 (1.0)	1
Plasma exchange, n (%)	0 (0)	1 (1.0)	1
Others, n (%)	3 (12.0)	10 (10.2)	0.73

PSL prednisolone

in Model 2 [HR 0.492 (0.323–0.750)]. On the other hand, death was associated with baseline eGFR and extra-renal lesions in both Model 1 [HR 0.715 (0.562–0.910) and HR 8.613 (2.296–32.310), respectively] and Model 2 [HR 0.714

(0.550–0.926) and HR 7.173 (1.427–36.065), respectively]. Next, to avoid the effect of the difference of baseline eGFR between C+ and C– groups, we also performed univariate and multivariate analyses, including 44 baseline-eGFR-matched patients (Supplemental Table 1–5). Clinical and histological characteristics in baseline eGFR-matched patients were similar with all tracked patients except baseline renal function. Kaplan–Meier method showed no significant difference in cumulative event rate of ESRD and/or death (Supplemental Figure). Cox regression analysis revealed baseline eGFR and extra-renal lesions to be the risk factors associated with renal and/or life prognoses [HR 0.244 (0.063–0.947) and HR 8.852 (1.102–71.133), respectively]. Competing risk analysis showed no significant factor in eGFR-matched patients, because of the small size of the model.

### Discussion

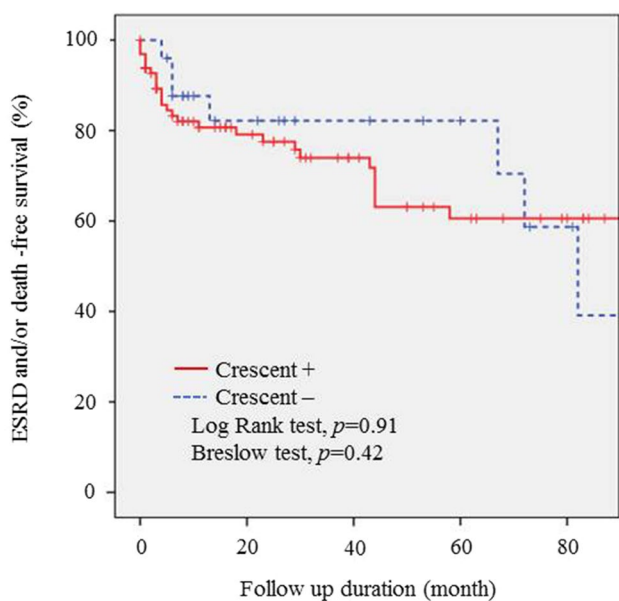
Here, clinicopathological features of ANCA-associated nephritis without crescent formation were clarified by a multicenter retrospective study. Clinically, ANCA-associated nephritis without crescent formation was characterized by better renal function at the time of renal biopsy with minor urinary abnormalities, but higher serum CRP level, higher frequency of extra-renal lesions of AAV, and lower frequency of renal-limited AAV. Pathologically, it had a higher frequency of arteritis. And there was no significant difference in renal and/or life prognosis regardless of crescent formation, suggesting that extra-renal lesions offset other prognostic factors. ANCA-associated nephritis without crescent formation had different clinicopathological features from those with crescent formation, suggesting the existence of an atypical subtype of ANCA-associated nephritis.

ANCA-associated nephritis without crescent formation had different clinical features compared to that with crescent formation. First, it had better baseline renal function with less proteinuria and hematuria. AAV with minor urinary abnormalities had been reported to have better renal function and lower frequency of crescent formation than that

**Table 4** Renal and overall survival between C– and C+ groups (all tracked patients)

	C– (n=25)	C+ (n=98)	p
Observational period, month (IQR)	26.0 (9.0–67.0)	23.0 (5.0–62.5)	0.47
Cr, mg/dl (IQR)	0.9 (0.8–1.4)	1.3 (0.9–2.2)	0.06
eGFR, ml/min/1.73 m <sup>2</sup> (IQR)	47.4 (35.0–62.5)	34.6 (21.4–51.5)	0.03
ESRD, n (%)	2 (8.0)	14 (14.3)	0.52
Death, n (%)	6 (24.0)	20 (20.4)	0.78
ESRD and/or death, n (%)	8 (32.0)	30 (30.6)	1

Cr creatinine, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, IQR interquartile range



No. at risk		
Crescent+	99	34
Crescent-	25	6

**Fig. 1** Cumulative rate of ESRD and/or death. Kaplan–Meier analysis did not show a significant difference in the cumulative rate of ESRD and/or death between C– and C+ groups

with major abnormalities [15]. It is reasonable to assume that minor glomerular damage would be associated with better renal function and less prominent urinary abnormalities.

Second, ANCA-associated nephritis without crescent formation had higher serum CRP level and frequencies of extra-renal lesions of AAV and arteritis. Furthermore, it included a lower frequency of renal-limited AAV. Arteritis is found in 13–23% of ANCA-associated nephritis [16–18]. As arteritis

is a focal lesion and sampling error of renal biopsies can occur, the true rates may be underestimated [5]. ANCA-associated glomerulonephritis with arteritis had higher serum CRP level and frequency of lung lesions [19]. Intra-renal vasculitis increased the likelihood of systemic vasculitis [5, 17]. These reports support our results showing that ANCA-associated nephritis without crescent formation had higher inflammation and frequency of renal arteritis with a higher frequency of systemic comorbidities of AAV. We considered that ANCA-associated nephritis without crescent formation predominantly affects larger vessels rather than glomerular capillaries, thereby developing more severe systemic inflammation that in turn promotes other organ involvement. This is compatible with the lower frequency of renal-limited AAV in ANCA-associated nephritis without crescent formation.

Third, there were no significant differences in renal or life prognosis between C– and C+ groups, suggesting that extra-renal lesions offset other prognostic factors. In predicting the renal prognosis of ANCA-associated glomerulonephritis, glomerular histopathological classification has been used widely [13]. Some validation studies of this classification have been performed and concluded similarly that focal class had the best, sclerotic class had the worst, and Mix and Crescentic classes had equal renal prognosis [14, 20, 21]. Meta-analysis showed that no racial differences existed with regard to these results [20]. In Japan, this classification was useful to stratify renal function and renal prognosis in a 2-year follow-up [22], despite the fact that the clinical features of Japanese and Western AAV patients differ, for example, with the MPA population and MPO-ANCA positivity being higher than GPA and PR3-ANCA ones in the former [23]. In addition, some other factors, such as age, renal function at the time of biopsy, and tubular atrophy, have been reported to associate with renal prognosis [24–26]. On the other hand,

**Table 5** Multivariable Cox regression analysis for ESRD/death; competing risk analysis for ESRD and death (all tracked patients)

	ESRD/Death		ESRD		Death	
	HR	95%CI	HR	95%CI	HR	95%CI
<b>(a) Model 1</b>						
Crescent	0.889	0.374–2.111	1.200	0.226–6.372	0.776	0.284–2.119
eGFR	0.661	0.541–0.809	0.488	0.333–0.713	0.715	0.562–0.910
Sclerotic class	2.539	0.988–6.523	4.165	1.289–13.454	0.580	0.070–4.807
Extra-renal lesions	3.689	1.645–8.274	1.616	0.534–4.895	8.613	2.296–32.310
<b>(b) Model 2</b>						
Crescent	1.096	0.408–2.943	2.170	0.240–19.627	0.938	0.295–2.985
eGFR	0.671	0.538–0.838	0.492	0.323–0.750	0.714	0.550–0.926
Sclerotic class	3.622	1.084–12.102	2.909	0.723–11.710	1.165	0.115–11.817
Extra-renal lesions	3.704	1.344–10.211	1.883	0.523–6.784	7.173	1.427–36.065
CRP	1.275	0.922–1.762	0.975	0.622–1.529	1.260	0.839–1.891

ESRD end-stage renal disease, HR hazard ratio, CI confidence intervals, eGFR estimated glomerular filtration rate, CRP C-reactive protein

it was reported that arteritis did not associate with ESRD and death [19]. In the present study, C– group had a significantly higher frequency of focal class and better renal function at the time of renal biopsy than C+ group. Despite the fact that these results were predictive of a better prognosis, and renal function at the last visit was better in C– group, Kaplan–Meier method showed no significant differences in cumulative event rates of ESRD and/or death. Consistent with the finding that the higher the rate of cellular crescents, the larger was the improvement of renal function observed [27], C– group showed less improvement after treatment than C+ group. However, C– group had a higher frequency of extra-renal lesions, which was considered to offset these positive prognostic factors in C– group. Especially, lung lesions have been reported to have a negative impact on life prognosis in AAV [23, 28]. These results should prompt us to pay especially careful attention to ANCA-associated nephritis without crescent formation despite its better renal function at the time of renal biopsy than that with crescent formation.

This study has some limitations: first, it is retrospective in nature. Second, treatment for AAV was not consistent as mentioned in Method. Third, sampling errors of renal biopsy, by which samples did not include crescents, may exist. Fourth, as we followed the definition of global glomerulosclerosis of a previous report [13], in which the cause was not considered, the possibility that global glomerulosclerosis was attributable to crescents could not be excluded. Fifth, there was a significant difference in the rates of tracked patients between C+ and C– groups. This might have biased the outcome despite the similarity seen in the characteristics at the time of renal biopsy between the tracked and all patients. Sixth, we can come up with no reasonable explanation for the trend that some patients in C– group reached the endpoint at around 70 months in the Kaplan–Meier curves.

In conclusion, C– group had atypical clinicopathological features including higher systemic inflammation and frequencies of renal arteritis and extra-renal lesions than C+ group. Although renal function at the time of renal biopsy was better in C– group, renal and life prognoses were similar to those of C+ group. These results suggested that ANCA-associated nephritis without crescent formation is a different subset from that with crescent formation, and as such requires special attention.

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### Compliance with ethical standards

**Conflict of interest** All the authors have declared no competing interests.

**Ethical approval** The study protocol was approved by the ethics committees of Kanazawa University Hospital (No. 2016-176).

**Informed consent** Informed consent was obtained from all individual participants included in this study.

### References

- Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65:1–11.
- Hauer HA, Bajema IM, van Houwelingen HC, et al. Renal histology in ANCA-associated vasculitis: differences between diagnostic and serologic subgroups. *Kidney Int.* 2002;61:80–9.
- Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis.* 2008;67:1004–100.
- Jennette JC, Thomas DB. Pauci-immune and antineutrophil cytoplasmic autoantibody-mediated crescentic Glomerulonephritis and vasculitis. In: Jennette JC, Olson JL, Silva FG, D'Agati VD, editors. *Heptinstall's pathology of the kidney.* 7th ed. Alphen aan den Rijn: Wolters Kluwer; 2015. p. 685–713.
- Joh K, Muso E, Shigematsu H, et al. Renal pathology of ANCA-related vasculitis: proposal for standardization of pathological diagnosis in Japan. *Clin Exp Nephrol.* 2008;12:277–91.
- Lockwood CM. Antineutrophil cytoplasmic autoantibodies: the nephrologist's perspective. *Am J Kidney Dis.* 1991;18:171–4.
- Nakabayashi K, Sumiishi A, Sano K, et al. Tubulointerstitial nephritis without glomerular lesions in three patients with myeloperoxidase-ANCA-associated vasculitis. *Clin Exp Nephrol.* 2009;13:605–13.
- D'Agati VD, Jennette JC, Silva FG. *Non-neoplastic kidney diseases.* Washington, DC: American Registry of Pathology; 2005.
- Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis.* 2007;66:222–7.
- Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis.* 2016;75:1583–94.
- Arimura Y, Muso E, Fujimoto S, et al. Evidence-based clinical practice guidelines for rapidly progressive glomerulonephritis 2014. *Clin Exp Nephrol.* 2016;20:322–41.
- Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* 2009;53:982–92.
- Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol.* 2010;21:1628–36.
- Bjørneklett R, Sriskandarajah S, Bostad L. Prognostic value of histologic classification of ANCA-associated glomerulonephritis. *Clin J Am Soc Nephrol.* 2016;11:2159–67.
- Hasegawa J, Hoshino J, Sekine A, et al. Clinical and pathological features of anti-neutrophil cytoplasmic antibody-associated vasculitis in patients with minor urinary abnormalities. *Nephrology.* 2018;23:1007–122.
- Jennette JC, Thomas DB. Crescentic glomerulonephritis. *Nephrol Dial Transplant.* 2001;16(Suppl 6):80–2.
- Vizjak A, Rott T, Koselj-Kajtina M, Rozman B, Kaplan-Pavlovic S, Ferluga D. Histologic and immunohistologic study and clinical presentation of ANCA-associated glomerulonephritis with

- correlation to ANCA antigen specificity. *Am J Kidney Dis.* 2003;41:539–49.
18. Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med.* 1985;56:467–83.
  19. Endo A, Hoshino J, Suwabe T, et al. Significance of small renal artery lesions in patients with antineutrophil cytoplasmic antibody-associated glomerulonephritis. *J Rheumatol.* 2014;41:1140–6.
  20. Chen YX, Xu J, Pan XX, et al. Histopathological classification and renal outcome in patients with antineutrophil cytoplasmic antibodies-associated renal vasculitis: a study of 186 patients and metaanalysis. *J Rheumatol.* 2017;44:304–13.
  21. Tanna A, Pusey CD. The histopathological classification of ANCA-associated glomerulonephritis comes of age. *J Rheumatol.* 2017;44:265–7.
  22. Yamagata K, Usui J, Nagata M, et al. Histopathological classification of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in a nationwide Japanese prospective 2-year follow-up cohort study. *Clin Exp Nephrol.* 2019;23:387–94.
  23. Yamagata K, Usui J, Saito C, et al. ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes. *Clin Exp Nephrol.* 2012;16:580–8.
  24. van de Lind Wijngaarden RA, Hauer HA, Wolterbeek R, et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol.* 2006;17:2264–74.
  25. Ford SL, Polkinghorne KR, Longano A, et al. Histopathologic and clinical predictors of kidney outcomes in ANCA-associated vasculitis. *Am J Kidney Dis.* 2014;63:227–35.
  26. Tanna A, Guarino L, Tam FW, et al. Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors. *Nephrol Dial Transplant.* 2015;30:1185–92.
  27. Vergunst CE, van Gurp E, Hagen EC, et al. An index for renal outcome in ANCA-associated glomerulonephritis. *Am J Kidney Dis.* 2003;41:532–8.
  28. Alba MA, Flores-Suárez LF, Henderson AG, et al. Interstitial lung disease in ANCA vasculitis. *Autoimmun Rev.* 2017;16:722–9.

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