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Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case–control study

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Abstract

Background: The coexistence of IgA nephropathy (IgAN) and antineutrophil cytoplasmic autoantibodies (ANCAs) is relatively rare. Only a few studies have reported the features of these patients.

Methods: We studied the clinical and histological features of 20 ANCA-positive IgAN patients. They were compared with ANCA-negative IgAN patients ($n = 40$) and ANCA-associated systemic vasculitis (AASV) patients ($n = 40$) with a randomly selected and matched proportion of crescentic glomeruli. Furthermore, 9 ANCA-positive crescentic IgAN patients out of the 20 cases were compared with two control groups with crescentic nephritis.

Results: ANCA-positive IgAN patients showed older age, lower haemoglobin and higher inflammatory indicator levels at baseline, and a higher percentage of general symptoms and pulmonary involvement, compared with ANCA-negative IgAN patients, and were comparable to AASV patients. Histologically, there was a significantly higher percentage of fibrinoid necrosis in glomeruli in ANCA-positive IgAN patients and in AASV patients compared with ANCA-negative IgAN patients (35, 25 and 0%, respectively, P = 0.003). After immunosuppressive therapy, ANCA-positive crescentic IgAN patients were more likely to withdraw from dialysis (75 versus 9.1%, P = 0.03) and not to reach end-stage renal disease within 6 months (11.1 versus 66.7%, P = 0.01) compared with ANCA-negative crescentic IgAN patients.

Conclusions: IgAN patients with ANCA positivity showed more severe clinical and histological features when compared with ANCA-negative IgAN patients and were comparable to AASV patients. However, renal prognosis was relatively better in ANCA-positive crescentic IgAN patients after aggressive immunosuppressive therapy in the short term, compared with ANCA-negative patients.

Key words: ANCA-associated systemic vasculitis, ANCA positive, antineutrophil cytoplasmic autoantibodies, IgA nephropathy

Introduction

IgA nephropathy (IgAN), characterized by mesangial IgA deposition, is the most prevalent form of primary glomerulonephritis. Antineutrophil cytoplasmic autoantibodies (ANCAs) are commonly linked to vasculitis and pauci-immune crescentic glomerulonephritis. However, the coexistence of IgAN and ANCA is relatively rare, in spite of their high incidences, separately. It is debatable whether IgG-ANCA plays a pathogenic role in IgAN.

No more than 30 cases with IgAN and coexisting IgG-ANCA positivity have been reported to date, mainly case reports [1–15] and two case series [16, 17]. O'Donoghue found that 2% of patients with IgAN showed serum IgG-ANCA positivity. The two patients had slowly progressive renal failure, without crescentic changes or focal necrosis in renal biopsies [1]. However, subsequent reports have presented a different picture. Haas *et al.* [16] reported findings on six ANCA-positive patients with IgAN, with crescents in more than 50% of glomeruli. The cases resembled ANCA-associated crescentic glomerulonephritis in both histological features and response to aggressive immunosuppressive therapy. Bantis *et al.* [17] studied eight ANCA-positive patients with IgAN, with more than 10% crescentic glomeruli, and reported more severe clinical manifestations and histological lesions, but better response to therapy, when compared with ANCA-negative patients. However, the former case series were confined to crescentic glomerulonephritis or were limited by small sample sizes and the lack of strict controls.

The main aim of the current study was to gain a deeper understanding of patients with IgAN and ANCA positivity. We summarized their clinical manifestations, histological features and response to treatment and prognosis, and compared them with ANCA-negative IgAN and ANCA-associated systemic vasculitis (AASV) patients.

Materials and methods

We retrospectively screened the clinical and histological data of 3543 patients with IgAN. The diagnosis of IgAN was based on the presence of dominant or codominant staining for IgA in the glomerular mesangium, from renal biopsy between January 1997 and December 2013 at the Renal Division of Peking University First Hospital. ANCAs were assessed in 1729 of these patients using indirect immunofluorescence assay and enzyme-linked immunosorbent assay. Twenty out of the 1729 IgAN patients were ANCA positive. ANCAs associated with propylthiouracil were excluded based on clinical data. The details of the recruitment process are shown in Supplementary data, Figure S1.

Clinical data at renal biopsy included serum creatinine level, proteinuria, blood pressure, haemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA) and immunosuppressive therapy. Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) two-level race equation. Systemic involvement included fever, fatigue, arthralgia, myalgia, long-standing sinusitis, otitis media episcleritis, keratitis, uveitis and retinal vasculitis despite antibiotic and antiallergy therapies. Pulmonary involvement was defined by the presence of cough, haemoptysis, pulmonary haemorrhage, respiratory failure or radiographic proof of infiltrates without evidence of infection [18].

Renal biopsy specimens were analysed and the following data were recorded: the proportion of glomeruli with cellular, fibrocellular or fibrous crescents, the presence of fibrinoid necrosis, the proportion of glomeruli with fibrinoid necrosis or global sclerosis, the presence of tubulointerstitial nephritis or ischaemic renal injury, the presence of IgA, IgG, IgM, C3, C1q and FRA deposits [graded on a scale of 0–3+ (0 for absence, + for mild, ++ for moderate and +++ for strong)]. Localization of deposits was observed by immunohistochemistry and electron microscopy.

We searched our follow-up databases (containing clinical, histological and follow-up data of patients with AASV or biopsy-proven IgAN from 1997 to 2013) for control group cases. Forty ANCA-negative patients with IgAN and 40 AASV patients were selected by stratified random sampling as two control

groups, with matching proportions of crescentic glomeruli. Two randomized control groups were chosen for the comparison of crescentic glomerulonephritis, including 18 patients with ANCA-negative crescentic IgAN and 18 patients with ANCA-associated crescentic glomerulonephritis, respectively.

Aggressive immunosuppressive therapy was defined as high-dose pulse methylprednisolone (7–15 mg/kg/day) plus cyclophosphamide therapy [19]. As for AASV, induction therapy included corticosteroids and cyclophosphamide [20]. Oral prednisone was prescribed at an initial dosage of 1 mg/kg/day for 4–6 weeks, reduced over time to 12.5–15 mg by 3 months, to 10 mg by 6–9 months and then to 5 mg by 18–24 months. Cyclophosphamide was administered either intravenously at a dosage of 0.7 gm/m^2 every month (usually six to nine pulses) or orally at a dosage of 2 mg/kg/day for 3–4 months. For patients older than age 65 years and those with renal insufficiency, the dose of cyclophosphamide was reduced by 25%. Patients with acute renal failure or pulmonary haemorrhage received three pulses of intravenous methylprednisolone (7–15 mg/kg/day) before induction of the therapy described above. For maintenance therapy, azathioprine was prescribed orally at a dosage of 2 mg/kg/day. The use of steroids and cyclophosphamide in rapidly progressive crescentic IgAN was analogous to the treatment of AASV [21].

Comparisons were made between ANCA-positive IgAN, ANCA-negative IgAN and AASV patients in clinical and histological features, response to treatment and prognosis. The follow-up endpoint was defined by death or the presence of end-stage renal disease (ESRD), including eGFR <15 mL/min/1.73 m², long-term dialysis or renal transplantation.

Normal distribution data were presented as average ± SD and non-normal distribution data as median (Q25, Q75). The baseline characteristics of the patients in the three groups were compared by ANOVA with *post hoc* analysis by Bonferroni correction for continuous variables and by χ^2 test or Fisher's exact test for nominal variables as appropriate. The rate of ESRD of the patients in the three groups was compared by log-rank test (Mantel–Cox test). Bonferroni correction was made for multiple comparison with the statistical significance threshold of 0.05/3 = 0.0167. The statistical analysis was performed by the SPSS (SPSS, Inc., Chicago, IL) statistical analysis program, version 19.0. A P-value <0.05 was considered to be statistically significant. A P-value <0.017 was considered to be statistically significant in *post hoc* analysis.

Results

Comparison among ANCA-positive IgAN, ANCA-negative IgAN and AASV patients with matched proportions of crescentic glomeruli

In this study, 1.2% (20/1729) of IgAN patients showed ANCA-positivity, including nine with crescentic glomerulonephritis (>50% crescentic glomeruli). Tables 1 and 2 and Figure 1 show the comparison of clinical and histological data, response to therapy and prognosis among ANCA-positive IgAN, ANCA-negative IgAN and AASV patients with matched proportions of crescentic glomeruli. The details of pulmonary involvement and coexistence with other autoimmune disease in ANCA-positive IgAN patients are shown in the Supplementary data.

There was a statistically significant difference in age among the groups (F = 29.326, P < 0.001). A Bonferroni *post hoc* test revealed that patients with ANCA-positive IgAN (52.3 ± 20.1 years, P < 0.001) and AASV (59.4 ± 13.7 years, P < 0.001) were notably older, compared with patients with ANCA-negative IgAN (34.6 ± 12.6 years). There was no statistically significant difference between the

Table 1. Comparison among ANCA-positive IgAN, ANCA-negative IgAN and AASV patients with matched proportions of crescentic glomeruli: baseline clinical data at renal biopsy

	ANCA-positive IgAN	ANCA-negative IgAN	AASV	P-value
No. of patients	20	40	40	
Age (years)	52.3 ± 20.1[a]	34.6 ± 12.6	59.4 ± 13.7[b]	<0.001
Gender (male, %)	45.0	60.0	60.0	0.48
ANCA	p 80.0%, c 20.0%		p 82.5%, c 15%, p + c 2.5%	0.81
BVAS	19.7 ± 3.8		20.5 ± 5.7	0.55
NS (%)	10.0	15.0	2.5	0.11
Gross haematuria	66.7[c]	22.5	15.0	0.04
Oliguria or anuria (%)	5.0	7.5	5.0	0.87
Crescentic glomerulonephritis (%)	45.0	45.0	45.0	1.00
MABP (mmHg)	103.5 ± 12.9	100.0 ± 11.7	99.4 ± 12.7	0.47
SCr (μmol/L)	255.4 (148.0, 389.2)	153.5 (89.5, 599.0)	246.5 (113.9, 508.8)	0.46
eGFR (mL/min/1.73 m²)	21.2 (10.9, 47.7)	47.0 (8.3, 87.1)	19.5 (9.2, 52.4)	0.12
UTP (g/24 h)	2.4 (1.1, 3.6)	3.4 (1.7, 5.8)	1.4 (0.8, 2.3)[b]	<0.001
Alb (g/L)	33.4 ± 5.5	33.3 ± 6.1	32.7 ± 4.6	0.86
HGB (g/L)	93.8 ± 20.8[a]	119.3 ± 28.6	93.6 ± 22.6[b]	<0.001
ESR (mm/h)	70.0 (17.0, 108.0)[a]	23.5 (8.5, 45.3)	75.0 (34.0, 110.0)[b]	<0.001
CRP (mg/L)	8.3 (2.6, 58.9)[a]	2.0 (1.4, 8.7)	25.7 (4.8, 91.5)[b]	<0.001
ANA positivity (%)	30.0[a]	0.0	15.0	0.001
Coexistence with other autoimmune disease (%)	25.0[a]	0.0	2.5	0.001
Systemic involvement (%)	90.0[a]	25.0	100.0[b]	<0.001
Lung involvement (%)	40.0[a]	0.0	70.0[b]	<0.001

Normal distribution data were presented as average ± SD and non-normal distribution data as median (Q25, Q75).
A P-value <0.0167 in *post hoc* analysis among groups: [a]ANCA-positive IgAN versus ANCA-negative IgAN; [b]ANCA-negative IgAN versus AASV; [c]ANCA-positive IgAN versus AASV.
ANCA, antineutrophil cytoplasmic autoantibody; p, p-ANCA, MPO-ANCA; c, c-ANCA, PR3-ANCA; p + c, p-ANCA + c-ANCA, MPO-ANCA + PR3-ANCA; IgAN, IgA nephropathy; BVAS, Birmingham vasculitis activity score; NS, nephrotic syndrome; MABP, mean arterial blood pressure; SCr, serum creatinine; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI two-level race equation; UTP, urinary total protein; Alb, serum albumin; HGB, haemoglobin; ESR, estimated sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody.

ANCA-positive IgAN and AASV groups (P = 0.28). Regarding the matched proportions of crescentic glomeruli, ANCA-positive IgAN patients showed a trend of lower eGFR compared with ANCA-negative IgAN patients, but were consistent with AASV patients at baseline [21.2 (10.9, 47.7) mL/min/1.73 m² versus 47.0 (8.3, 87.1) mL/min/1.73 m² versus 19.5 (9.2, 52.4) mL/min/1.73 m², P = 0.12]. The percentage of patients with systemic symptoms was higher in ANCA-positive IgAN patients than in ANCA-negative IgAN patients (90.0 versus 25.0%, P < 0.001), and was comparable to AASV patients (90.0 versus 100.0%, P = 0.11). Forty percent of patients with ANCA positivity showed pulmonary involvement; the percentage was higher in this group than in ANCA-negative IgAN patients (40.0 versus 0.0%, P < 0.001), and comparable to AASV patients (40.0 versus 70.0%, P = 0.03). There were statistically significant differences in haemoglobin levels (F = 12.405, P < 0.001), ESR (P < 0.001) and CRP (P < 0.001) among the three groups (shown in the Supplementary data).

Histologically, no statistical difference was seen in the composition of crescents within the three groups. Notably, there were statistically significant differences among the groups in the presence of fibrinoid necrosis (P = 0.003). The percentage of patients with fibrinoid necrosis was higher in ANCA-positive IgAN patients (35.0 versus 0.0%, P = 0.002) and AASV patients (25.0 versus 0.0%, P = 0.004) when compared with ANCA-negative IgAN patients.

After aggressive immunosuppressive therapy, 75.0% (3/4) of ANCA-positive IgAN patients withdrew from dialysis, while there were no withdrawals among the ANCA-negative IgAN cases (75.0 versus 0.0%, P = 0.01). However, there was no statistical difference in the rate of ESRD among the three groups at 6 months after renal biopsy (P = 0.09) or at the end of follow-up (P = 0.52).

Comparison among ANCA-positive crescentic IgAN, ANCA-negative crescentic IgAN and ANCA-associated crescentic glomerulonephritis patients (simple random sampling)

Nine out of 20 ANCA-positive IgAN patients were diagnosed with crescentic IgAN. Tables 3 and 4 and Figure 2 show the comparison of clinical and histological data, response to therapy and prognosis among ANCA-positive crescentic IgAN, ANCA-negative crescentic IgAN and ANCA–associated crescentic glomerulonephritis patients (simple random sampling).

There was a statistically significant difference in age among the groups (F = 8.281, P = 0.001). ANCA-associated crescentic glomerulonephritis patients (59.4 ± 10.2 years, P = 0.001) were older compared with patients with ANCA-negative crescentic IgAN (40.8 ± 15.1 years). However, there was no statistically significant difference in age between ANCA-positive crescentic IgAN and ANCA-negative crescentic IgAN patients (54.8 ± 18.0 years versus 40.8 ± 15.1 years, P = 0.06), and between ANCA-positive crescentic IgAN and ANCA-associated crescentic glomerulonephritis patients (54.8 ± 18.0 years versus 59.4 ± 10.2 years, P = 1.00). No statistical difference was found in eGFR among the three groups (P = 0.46). There were more ANCA-positive crescentic IgAN cases accompanied by systemic symptoms (66.7 versus 5.6%, P = 0.002) and pulmonary involvement (44.4 versus 0.0%, P = 0.007) than in the ANCA-negative crescentic IgAN patients, and this was in accordance with AASV patients (66.7 versus 100.0%, P = 0.33; 44.4 versus 77.8%, P = 0.38). There were statistically significant differences among the groups in haemoglobin levels (F = 6.866, P = 0.003) and CRP (P = 0.007). Further details can be found in the Supplementary data.

Table 2. Comparison among ANCA-positive IgAN, ANCA-negative IgAN and AASV patients with matched proportions of crescentic glomeruli: histological data, treatment and prognosis

	ANCA-positive IgAN	ANCA-negative IgAN	AASV	P-value
No. of patients	20	40	40	
Timing of biopsy in respect to onset of symptoms (months)	6.0 (2.3, 48.0)	5.0 (2.0, 20.5)	3.0 (1.5, 7.0)	0.11
Therapy previous to biopsy				
Corticosteroids (%)	75.0[a]	17.5	80.0[b]	<0.001
Pulse methylprednisolone (7–15 mg/kg/day) (%)	25.0	2.5	32.5[b]	0.002
Cyclophosphamide (%)	20.0	27.5	17.5	0.03
Dialysis (%)	20.0	20.0	22.5	0.78
Plasma exchange (%)	0.0	0.0	7.5	0.06
Glomeruli with crescents (%)	44.3 (21.5, 76.1)	44.7 (12.7, 76.9)	42.7 (16.5, 77.2)	0.85
Glomeruli with cellular crescents (%)	8.3 (0.0, 19.3)	5.9 (0.0, 20.0)	14.6 (0.0, 24.7)	0.50
Glomeruli with fibrocellular crescents (%)	17.0 (5.2, 49.3)	21.9 (5.7, 37.1)	5.2 (0.0, 30.2)	0.14
Glomeruli with fibrous crescents (%)	1.2 (0.0, 12.7)	0.0 (0.0, 8.5)	0.0 (0.0, 16.8)	0.66
Global sclerosis (%)	3.6 (0.0, 11.0)	9.1 (0.0, 22.4)	0.0 (0.0, 5.0)[b]	0.002
Presence of fibrinoid necrosis (%)	35.0[a]	0.0	25.0[b]	0.003
Glomeruli with fibrinoid necrosis (%)	3.9 (2.7, 7.4)		6.9 (4.0, 17.0)	0.11
TIN or ischaemic kidney injury (%)	5.0	17.5	5.0	0.13
Haemodialysis (%)	25.0	22.5	25.0	1.00
Withdraw from dialysis (%)	75.0 (3/4)[a]	0.0 (0/9)	30.0 (3/10)	0.01
Corticosteroids and/or cyclophosphamide (%)	95.0[a]	64.9	95.0[b]	<0.001
Plasma exchange (%)	0.0	0.0	12.5	0.02
Follow-up period (months)	7.0 (1.0, 52.5)	25.5 (0.0, 44.3)	25.5 (3.5, 67.5)	0.35
ESRD within 6 months (% events)	10.0	27.5	12.5	0.13
ESRD within 6 months (events per person-year)	0.26	0.77	0.31	0.09
ESRD (% events)	40.0	35.0	27.5	0.59
ESRD (events per person-year)	0.12	0.14	0.08	0.52
Mortality (% events)	10.0	7.5	25.0	0.07
Mortality (events per person-year)	0.04	0.02	0.07	0.19

Normal distribution data were presented as average ± SD and non-normal distribution data as median (Q25, Q75).
A P-value <0.0167 in *post hoc* analysis among groups: [a]ANCA-positive IgAN versus ANCA-negative IgAN; [b]ANCA-negative IgAN versus AASV; [c]ANCA-positive IgAN versus AASV.
ANCA, antineutrophil cytoplasmic autoantibody; IgAN, IgA nephropathy; TIN, tubulointerstitial nephritis; ESRD, end-stage renal disease.
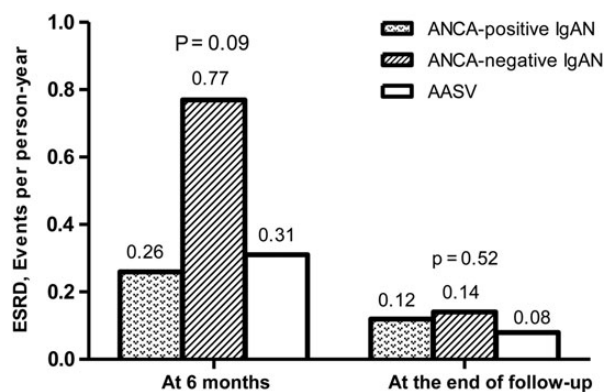

Fig. 1. ESRD in ANCA-positive IgAN, ANCA-negative IgAN and AASV patients with matched proportions of crescentic glomeruli. ANCA, antineutrophil cytoplasmic autoantibody; IgAN, IgA nephropathy; AASV, ANCA-associated systemic vasculitis; ESRD, end-stage renal disease.

There were statistically significant differences among the three groups in the presence of fibrinoid necrosis (P = 0.01). The percentage of patients with fibrinoid necrosis was higher in the ANCA-positive crescentic IgAN patients (44.4 versus 0.0%, P = 0.007) and ANCA-associated crescentic glomerulonephritis patients (33.0 versus 0.0%, P = 0.02) when compared with the ANCA-negative crescentic IgAN patients.

After aggressive immunosuppressive therapy, a statistically significant difference was obtained in the short-term rate of ESRD (P = 0.02). We made a comparison between each of the two groups, and found ANCA-positive crescentic IgAN patients had lower rates of ESRD within 6 months, compared with ANCA-negative crescentic IgAN patients (P = 0.015). There was no statistical difference between ANCA-positive crescentic IgAN glomerulonephritis and ANCA-associated crescentic glomerulonephritis (P = 0.20), ANCA-negative crescentic IgAN glomerulonephritis and ANCA-associated crescentic glomerulonephritis (P = 0.05). A statistically significant difference was also observed in the proportion of patients who withdrew from dialysis within the groups (P = 0.05). Within the ANCA-positive crescentic IgAN group, 75.0% (3/4) of patients withdrew from dialysis, while only 9.1% (1/11) of patients in the ANCA-negative crescentic IgAN group withdrew from dialysis (75.0 versus 9.1%, P = 0.03). However, at the end of follow-up, there was no statistical difference in the rate of ESRD among the three groups (P = 0.11).

Discussion

In the current study, we summarized the clinical and histological characteristics, the response to treatment and prognosis of 20 ANCA-positive IgAN patients, including 9 cases with crescentic glomerulonephritis. Compared with ANCA-negative IgAN patients, ANCA-positive IgAN patients showed a more severe clinical picture, but a better response to aggressive immunosuppressive therapy and better renal outcomes in the short-term.

Table 3. Comparison among ANCA-positive crescentic IgAN, ANCA-negative crescentic IgAN and ANCA-associated crescentic glomerulonephritis patients (simple random sampling): baseline clinical data at renal biopsy

	ANCA-positive crescentic IgAN	ANCA-negative crescentic IgAN	ANCA-associated crescentic glomerulonephritis	P-value
No. of patients	9	18	18	
Age (years)	54.8 ± 18.0	40.8 ± 15.1	59.4 ± 10.2[a]	0.001
Gender (male, %)	33.3	72.2	61.1	0.15
ANCA	p 89%, c 11%		p 78%, c 22%	0.64
BVAS	18.3 ± 3.4		21.2 ± 4.9	0.14
NS (%)	22.2	27.8	16.7	0.90
Gross haematuria (%)	66.7	27.8	22.2	0.06
Oliguria or anuria (%)	0.0	11.1	16.7	0.61
MABP (mmHg)	107.0 ± 11.9	102.0 ± 12.0	98.7 ± 10.1	0.21
SCr (μmol/L)	427.6 ± 265.2	531.9 ± 327.0	631.7 ± 398.3	0.35
eGFR (mL/min/1.73 m²)	20.2 (5.75, 21.2)	10.6 (6.1, 36.9)	6.8 (5.6, 14.1)	0.46
UTP (g/24 h)	2.6 (1.8, 5.5)	5.5 (3.9, 7.2)	2.4 (1.1, 3.4)[a]	0.005
Alb (g/L)	32.5 ± 6.1	31.9 ± 5.0	31.3 ± 4.3	0.83
HGB (g/L)	80.7 ± 15.1	102.2 ± 17.4	80.0 ± 21.3[a]	0.003
ESR (mm/h)	93.5 (27.5, 123.8)	48.5 (23.1, 82.5)	64.0 (46.5, 101.5)	0.24
CRP (mg/L)	13.0 (4.1, 53.8)	2.0 (1.0, 10.0)	17.8 (13.2, 61.8)[a]	0.007
ANA positivity (%)	22.2	0.0	16.7	0.07
Coexistence with other autoimmune disease (%)	22.2	5.6	5.6	1.00
Systemic involvement (%)	66.7[b]	5.6	100.0[a]	<0.001
Lung involvement (%)	44.4[b]	0.0	77.8[a]	<0.001

Normal distribution data were presented as average ± SD and non-normal distribution data as median (Q25, Q75).
A P-value <0.0167 in *post hoc* analysis among groups: [a]ANCA-negative crescentic IgAN versus ANCA-associated crescentic glomerulonephritis; [b]ANCA-positive crescentic IgAN versus ANCA-negative crescentic IgAN; [c]ANCA-positive crescentic IgAN versus ANCA-associated crescentic glomerulonephritis.
ANCA, antineutrophil cytoplasmic autoantibody p, p-ANCA, MPO-ANCA; c, c-ANCA, PR3-ANCA; p + c, p-ANCA + c-ANCA, MPO-ANCA + PR3-ANCA; IgAN, IgA nephropathy; BVAS, birmingham vasculitis activity score; NS, nephrotic syndrome; MABP, mean arterial blood pressure; SCr, serum creatinine; eGFR, estimated glomerular filtration rate calculated using the CKD-EPI two-level race equation; UTP, urinary total protein; Alb, serum albumin; HGB, haemoglobin; ESR, estimated sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody.

Furthermore, the clinical features were quite similar between ANCA-positive IgAN patients and AASV patients.

Some studies have indicated that the presence of immunoglobulin deposits in renal specimens might be the early stage of typical pauci-immune ANCA-associated glomerulonephritis [18]. Immune complexes containing IgA might initiate an inflammatory reaction that was augmented in the presence of ANCA, which should then be degraded rapidly by enzymes. However, Bantis *et al.* [17] observed that IgA deposits were still present in renal biopsy specimens 6 months after treatment. In addition, we found that some features of ANCA-positive IgAN patients partially resembled IgAN patients, such as gross haematuria, which distinguished them from AASV. Therefore, the IgA deposits in these patients could not be explained as a transient phenomenon of AASV. However, whether immune complex containing IgA could lead to production of ANCA remains debated. Elevation of serum tumour necrosis factor-α, soluble forms of intercellular adhesion molecule 1 and urinary interleukin-8 levels could be detected in the acute or deteriorating phase of IgAN [22–24], which could possibly result in the activation of polyclonal B cells and in the formation of ANCA [15]. However, we found that IgAN patients with ANCA positivity were relatively older than ANCA-negative patients, and the presence of ANCA was rarely seen even in the acute or deteriorating phase of IgAN. Therefore, it seemed that immune complex containing IgA in ANCA-positive IgAN patients was not the direct pathogenesis of ANCA production.

In our study, in contrast to ANCA-negative IgAN patients, ANCA-positive IgAN patients were notably older, showed worse renal function, manifested with more systemic symptoms and pulmonary involvement, and they showed obvious abnormality in inflammatory indicators and lower haemoglobin levels, which were consistent with the findings in AASV patients. We observed fibrinoid necrosis in ANCA-positive IgAN patients, which was also comparable to AASV patients, as ANCA was commonly considered to be associated with necrosis lesions. Half of the patients reported by Haas *et al.* [16] (3/6) and Bantis *et al.* [17] (4/8) also showed focal and segmental necrotizing lesions. With matched proportions of glomeruli with crescents, ANCA-positive IgAN patients showed worse renal function at renal biopsy, but tended to have a better response to aggressive immunosuppressive therapy in the short-term and a greater possibility of withdrawal from dialysis, when compared with ANCA-negative patients, and were similar to patients with AASV. After immunosuppressive therapy, most of the case reports showed an optimistic response to therapy. Haas *et al.* [16] found that two patients showed preserved renal function and one patient discontinued dialysis. Bantis *et al.* [17] also observed stable renal function in all eight cases. ANCA-positive IgAN patients were more similar to AASV patients than ANCA-negative IgAN patients in both clinical and histological features. Therefore, we speculated that ANCA played a more important role in the acute phase in ANCA-positive IgAN patients. The possibility that ANCA-positive IgAN patients developed coincidental ANCA-associated glomerulonephritis in addition to pre-existing latent IgAN could be one reasonable explanation, considering the high morbidity of IgAN and our observations in the current study.

Inconsistent with the long-term stable renal function found by Bantis *et al.* [17], no statistically significant differences were found in renal outcomes at the end of follow-up, and ~40% of ANCA-positive IgAN patients progressed to ESRD at the end of this study. However, the proportion of glomeruli with crescents was relatively lower and there were no patients on dialysis at

Table 4. Comparison among ANCA-positive crescentic IgAN, ANCA-negative crescentic IgAN and ANCA-associated crescentic glomerulonephritis patients (simple random sampling): histological data, treatment and prognosis

	ANCA-positive crescentic IgAN	ANCA-negative crescentic IgAN	ANCA–associated crescentic glomerulonephritis	P-value
No. of patients	9	18	18	
Timing of biopsy in respect to onset of symptoms (months)	3.0 (2.0, 48.0)	3.0 (1.2, 6.0)	2.3 (1.5, 3.8)	0.52
Therapy previous to biopsy				
Corticosteroids (%)	66.7[a]	11.1	77.8[b]	<0.001
Pulse methylprednisolone (7–15 mg/kg/day) (%)	33.3	11.1	38.9	0.13
Cyclophosphamide (%)	11.1	5.6	11.1	0.80
Dialysis (%)	33.3	55.6	38.9	0.46
Plasma exchange (%)	0.0	0.0	0.0	
Glomeruli with crescents (%)	79.4 ± 12.9	71.9 ± 17.9	76.4 ± 14.3	0.47
Glomeruli with cellular crescents (%)	14.9 (3.3, 27.6)	14.1 (6.1, 25.6)	19.2 (4.4, 49.4)	0.55
Glomeruli with fibrocellular crescents (%)	50.0 (18.2, 66.1)	38.3 (27.8, 49.6	14.9 (4.4, 35.3)	0.03
Glomeruli with fibrous crescents (%)	6.3 (0.0, 30.2)	10.5 (0.0, 19.5)	4.6 (0.0, 54.8)	0.97
Global sclerosis (%)	3.1 (0.0, 10.3)	9.3 (0.0, 20.1)	0.0 (0.0, 3.1)[b]	0.01
Presence of fibrinoid necrosis (%)	44.4[a]	0.0	33.3	0.01
Glomeruli with fibrinoid necrosis (%)	3.1 (1.5, 3.6)		14.9 (8.5, 22.5)	0.10
TIN or ischaemic kidney injury (%)	0.0	11.1	5.6	0.80
Haemodialysis (%)	44.4	61.1	55.6	0.71
Withdrawl from dialysis (%)	75.0 (3/4)	9.1 (1/11)	30.0 (3/10)	0.05
Corticosteroids and /or cyclophosphamide (%)	100.0	88.9	94.4	0.80
Plasma exchange (%)	0.0	0.0	16.7	0.21
Follow-up period (months)	9.0 (2.0, 16.0)	1.5 (0.0, 26.0)	7.5 (1.0, 30.0)	0.25
ESRD within 6 months (% events)	11.1[a]	66.7	38.9	0.02
ESRD within 6 months (events per person-year)	0.31[a]	2.94	1.31	0.02
ESRD (% events)	44.4	72.2	44.4	0.19
ESRD (events per person-year)	0.36	0.56	0.28	0.11
Mortality (% events)	11.1	11.1	27.8	0.53
Mortality (events per person-year)	0.08	0.08	0.17	0.57

Normal distribution data were presented as average ± SD and non-normal distribution data as median (Q25, Q75).
A P-value <0.0167 in *post hoc* analysis among groups: [a]ANCA-positive crescentic IgAN versus ANCA-negative crescentic IgAN; [b]ANCA-negative crescentic IgAN versus ANCA-associated crescentic glomerulonephritis; [c]ANCA-positive crescentic IgAN versus ANCA-associated crescentic glomerulonephritis.
ANCA, antineutrophil cytoplasmic autoantibody; IgAN, IgA nephropathy; TIN, tubulointerstitial nephritis; ESRD, end-stage renal disease.
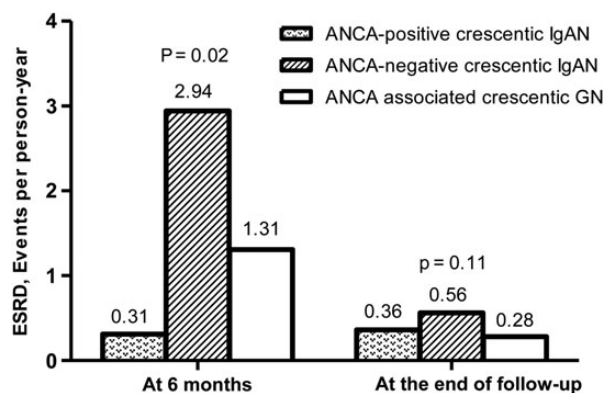

Fig. 2. ESRD in ANCA-positive crescentic IgAN, ANCA-negative crescentic IgAN and ANCA-associated crescentic glomerulonephritis patients (simple random sampling). ANCA, antineutrophil cytoplasmic autoantibody; IgAN, IgA nephropathy; ESRD, end-stage renal disease; GN, glomerulonephritis.

baseline in the case series of Bantis *et al.* [17]. ANCA-positive IgAN patients did not show better renal outcomes in the long term, probably because of their increased age and the overlapping of two pathogenic factors.

It should be noted that 51.2% of patients with biopsy-proven IgAN were not tested for ANCA in our centre, so there might be bias in the evaluation of the incidence rate of ANCA positivity in IgAN. However, 80% (16/20) of the ANCA-positive IgAN patients involved in the current study were admitted to our centre in the last 7 years, and there was a high percentage (72%) of ANCA testing in IgAN patients during this time. To the best of our knowledge, the current study was the largest series of ANCA-positive IgAN patients studied to date, and we compared the patients with strict control groups, which were lacking in previous studies. Therefore, our study provides more comprehensive information for physicians about patients with IgAN and ANCA positivity.

In conclusion, we performed a retrospective case–control study and found that ANCA-positive IgAN patients, used to show overlapping of AASV and IgAN, presented a more severe clinical and histological picture than ANCA-negative IgAN patients, and their renal outcomes were relatively better with aggressive immunosuppressive therapy in the short term. We suggest that screening for ANCA should be taken into consideration in certain IgAN patients, especially in elderly patients, and patients with severe clinical manifestations, systemic symptoms or fibrinoid necrosis in renal biopsy.

Supplementary data

Supplementary data are available online at http://ckj.oxford journals.org.

Conflict of interest statement

None declared.

(See related articles by Rojas-Rivera *et al*. Rapidly progressive IgA nephropathy: a form of vasculitis or a complement-mediated disease? *Clin Kidney J* (2015) 8: 477–481 and by Ring *et al*. Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum? *Clin Kidney J* (2015) 8: 489–491.)

References

1. O'Donoghue DJ, Nusbaum P, Noel LH *et al*. Antineutrophil cytoplasmic antibodies in IgA nephropathy and Henoch–Schonlein purpura. *Nephrol Dial Transplant* 1992; 7: 534–538
2. Allmaras E, Nowack R, Andrassy K *et al*. Rapidly progressive IgA nephropathy with anti-myeloperoxidase antibodies benefits from immunosuppression. *Clin Nephrol* 1997; 48: 269–273
3. Ramirez SB, Rosen S, Niles J *et al*. IgG antineutrophil cytoplasmic antibodies in IgA nephropathy: a clinical variant? *Am J Kidney Dis* 1998; 31: 341–344
4. Rollino C, Mazzucco G, Basolo B *et al*. cANCA positivity in a case of IgA glomerulonephritis (IgAGN) with necrotizing lesions. *Nephrol Dial Transplant* 1999; 14: 797–798
5. Vrtovsnik F, Queffeulou G, Skhiri H *et al*. Simultaneous IgA nephropathy and Wegener's granulomatosis—overlap or co-incidence (the role of renal biopsy). *Nephrol Dial Transplant* 1999; 14: 1266–1267
6. Tagboto S, Carr S, Varghese A *et al*. Iga nephropathy, antineutrophil cytoplasmic antibodies and crescentic glomerulonephritis in a patient with the Hermansky–Pudlak syndrome. *Am J Nephrol* 2001; 21: 58–62
7. Lui SL, Chan KW, Yip PS *et al*. Simultaneous occurrence of diabetic glomerulosclerosis, IgA nephropathy, crescentic glomerulonephritis, and myeloperoxidase-antineutrophil cytoplasmic antibody seropositivity in a Chinese patient. *Am J Kidney Dis* 2002; 40: E14
8. Ogawa N, Yano S, Yamane Y *et al*. MPO-ANCA-positive IgA nephropathy successfully treated with tonsillectomy. *Clin Exp Nephrol* 2007; 11: 326–331
9. Uchiyama M, Akahoshi T, Matsui T *et al*. Crescentic glomerulonephritis with antimyeloperoxidase antibodies developing during the course of IgA nephropathy in a patient with rheumatoid arthritis. *Mod Rheumatol* 2001; 11: 76–79
10. Amir AR, Sheikh SS. ANCA-associated crescentic IgA glomerulonephritis in pregnancy. *J Nephrol* 2002; 15: 716–719
11. Rocco VK, Horn RG, Fogo AB. Quiz page. IgA nephropathy and superimposed pauci-immune necrotizing crescentic glomerulonephritis, the latter clinically typical of Wegener's granulomatosis. *Am J Kidney Dis* 2002; 40: xli
12. Winters MJ, Hurley RM, Lirenman DS. ANCA-positive glomerulonephritis and IgA nephropathy in a patient on propylthiouracil. *Pediatr Nephrol* 2002; 17: 257–260
13. Ku E, Ananthapanyasut W, Campese VM. IgA nephropathy in a patient with ulcerative colitis, Graves' disease and positive myeloperoxidase ANCA. *Clin Nephrol* 2012; 77: 146–150
14. Ozkok A, Sirin BM, Elcioglu OC *et al*. Crescentic glomerulonephritis due to IgA nephropathy or propylthiouracil-induced_ Mpo-Anca positive vasculitis? *Ren Fail* 2013; 35: 930
15. Shimizu M, Wada T, Sakai N *et al*. Clinicopathological features of antineutrophil cytoplasmic antibodies associated vasculitis in Japanese patients with IgA nephropathy. *Clin Exp Nephrol* 2000; 4: 251–256
16. Haas M, Jafri J, Bartosh SM *et al*. ANCA-associated crescentic glomerulonephritis with mesangial IgA deposits. *Am J Kidney Dis* 2000; 36: 709–718
17. Bantis C, Stangou M, Schlaugat C *et al*. Is presence of ANCA in crescentic IgA nephropathy a coincidence or novel clinical entity? A case series. *Am J Kidney Dis* 2010; 55: 259–268
18. Yu F, Chen M, Wang SX *et al*. Clinical and pathological characteristics and outcomes of Chinese patients with primary anti-neutrophil cytoplasmic antibodies-associated systemic vasculitis with immune complex deposition in kidney. *Nephrology (Carlton)* 2007; 12: 74–80
19. Lv J, Yang Y, Zhang H *et al*. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. *J Am Soc Nephrol* 2013; 24: 2118–2125
20. Li ZY, Chang DY, Zhao MH *et al*. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 439 cases in a single Chinese center. *Arthritis Rheumatol* 2014; 66: 1920–1926
21. KDIGO clinical practice guideline for glomerulonephritis: immunoglobulin A nephropathy. *Kidney Int Suppl (2011)* 2012; 2: 209–217
22. Yokoyama H, Takaeda M, Wada T *et al*. Glomerular ICAM-1 expression related to circulating TNF-alpha in human glomerulonephritis. *Nephron* 1997; 76: 425–433
23. Yokoyama H, Wada T, Furuichi K *et al*. Urinary levels of chemokines (MCAF/MCP-1, IL-8) reflect distinct disease activities and phases of human IgA nephropathy. *J Leukoc Biol* 1998; 63: 493–499
24. Wada T, Yokoyama H, Tomosugi N *et al*. Detection of urinary interleukin-8 in glomerular diseases. *Kidney Int* 1994; 46: 455–460