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Clinical significance of ANCA positivity in patients with IgA vasculitis: a retrospective monocentric study

Jae Yeon Kim[1] · Hyeok Choi[1] · Minyoung Kevin Kim[1] · Soo Bin Lee[1] · Yong-Beom Park[2,3] ·
Sang-Won Lee[2,3]

Abstract

We assessed the detection rate of antineutrophil cytoplasmic antibody (ANCA) and investigated the clinical significance of ANCA positivity at diagnosis in patients with IgA vasculitis (Henoch-Schönlein purpura). We retrospectively reviewed their medical records of 86 IgA vasculitis patients. We divided IgA vasculitis patients based on ANCA positivity and compared variables at diagnosis and poor outcomes and medication during follow-up between the two groups. All-cause mortality, relapse, chronic kidney disease (CKD) (stage 3–5) and end-stage renal disease (ESRD) were defined as poor outcomes. We assessed the renal histological features based on the International Study of Kidney Disease in Children (ISKDC) classification and Oxford classification. Comparison of cumulative survivals was analysed by the Kaplan–Meier survival analysis. Five of 86 IgA vasculitis patients (5.8%) had ANCA and all ANCA-positive patients had myeloperoxidase (MPO)-ANCA. IgA vasculitis patients with ANCA exhibited pulmonary and nervous involvement of IgA vasculitis more frequently than those without. There was no significant difference in renal involvement between the two groups. There were no significant differences in renal histological features and poor outcomes related to renal function between IgA vasculitis patients with and without ANCA. In addition, 5 IgA vasculitis patients did not meet the classification criteria for ANCA-associated vasculitis (AAV). Particularly, there were no significant differences in CKD and ESRD-free survival rates between IgA vasculitis patients with and without ANCA. 5.8% of IgA vasculitis patients had MPO-ANCA and poor outcomes of IgA vasculitis were not affected by the presence of ANCA.

Keywords Antineutrophil cytoplasmic antibody · Vasculitis · IgA vasculitis · Prognosis

Introduction

IgA vasculitis, that is identically called Henoch-Schönlein purpura, is a systemic autoimmune vasculitis which primarily affects small-sized vessels including capillaries, arterioles and venules [1]. IgA vasculitis is characterised by various clinical manifestations: arthralgia/arthritis, abdominal

✉ Sang-Won Lee
  sangwonlee@yuhs.ac

  Jae Yeon Kim
  hey3@hanmail.net

  Hyeok Choi
  hyeokchoi@yonsei.ac.kr

  Minyoung Kevin Kim
  kevmin87@gmail.com

  Soo Bin Lee
  soobinl22@naver.com

  Yong-Beom Park
  YONGBPARK@yuhs.ac

1 Deparment of Medicine, Yonsei University College
   of Medicine, Seoul, Republic of Korea

2 Division of Rheumatology, Department of Internal Medicine,
   Yonsei University College of Medicine, 50-1 Yonsei-ro,
   Seodaemun-gu, Seoul 03722, Republic of Korea

3 Institute for Immunology and Immunological Diseases,
   Yonsei University College of Medicine, Seoul,
   Republic of Korea

pain, glomerulonephritis, lung lesions and neuropathies may occur based on skin purpura [1, 2]. IgA vasculitis commonly occurs in patients of age under 20 years and the annual incidence in children ranges from 10 to 20 cases of 100,000 patients per year, while that in adults is as lower as 1.3 cases of 100,000 patients per year [3, 4]. Early kidney involvement of IgA vasculitis may provoke seriously poor outcomes during follow-up such as relapse, chronic kidney disease (CKD) and end-stage renal disease (ESRD) [5, 6].

According to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (the 2012 CHCC definitions), small vessel vasculitis can be divided into two categories such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune complex vasculitis characterised by immune complex deposits [1, 7]. IgA vasculitis is one of immune complex vasculitis and described as vasculitis with IgA1 and complement 3 (C3)-dominant immune deposits. Thus, ANCA may theoretically be rarely detected in patients with IgA vasculitis. For this reason, so far, there have been only a few case reports on ANCA-positive IgA vasculitis patients to date [8]. However, there was no report on the clinical implication of ANCA in a considerable number of adult patients with IgA vasculitis yet. Hence, in this study, we assessed the detection rate and the subtype of ANCA and investigated the clinical significance of ANCA positivity at diagnosis in patients with IgA vasculitis. Furthermore, we reclassified IgA vasculitis patients with ANCA based on the classification criteria for both IgA vasculitis and AAV.

Patients and methods

Patients

We collected the list of 97 patients with IgA vasculitis using the Clinical Data Repository System and retrospectively reviewed their medical records. The inclusion and exclusion criteria were as follows: (1) patients who had been first classified as IgA vasculitis at the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from March 2005 to January 2019; (2) patients who fulfilled the European League against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria for IgA vasculitis. Since the American College of Rheumatology criteria for IgA vasculitis has an item of age ≤ 20 years at disease onset and our study included only adult patients, we utilised the EULAR/PRINTO/PRES criteria. The EULAR/PRINTO/PRES criteria consist of mandatory palpable purpura, not thrombocytopenia/petechiae and more than one of the four conditions such as diffuse abdominal pain, typical leukocytoclastic vasculitis with

predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposit on histology, arthritis or arthralgia and renal involvement (proteinuria: > 0.3 g/24 h or > 30 mmol/mg of urine albumin to creatinine ratio on a spot morning sample; and/or haematuria, red blood cell (RBC) casts: > 5 RBC per high power field or ≥ 2 + on dipstick or RBC casts in the urinary sediment) [9]; (3) patients who had well-documented medical records to collect clinical and laboratory data at diagnosis of IgA vasculitis and to confirm the fulfilment of the classification criteria; (4) patients who had the results of both indirect immunofluorescence assay and antigen-specific assay for ANCA such as perinuclear (P)-ANCA, C-ANCA, MPO-ANCA and proteinase 3 (PR3)-ANCA at diagnosis. In patients who tested positive by indirect fluorescence assay but negative by antigen-specific assays, P-ANCA positive was considered as MPO-ANCA positive and C-ANCA positive as PR3-ANCA; (5) patients who had been followed up for at least ≥ 12 weeks; (6) patients who had never been classified as other vasculitis other than IgA vasculitis or medical history to affect either the classification of IgA vasculitis or ANCA positivity prior to or at diagnosis, particularly, chronic liver diseases, coexisting malignancies, serious comorbidities and serious infection, which were identified by the 10th revised International Classification Diseases (ICD-10); (7) patients who had never received immunosuppressive drugs for IgA vasculitis prior to diagnosis, which might be related to ANCA positivity and were verified by the Korean Drug Utilisation Review (DUR) system.

Of 97 patients screened, we excluded five IgA vasculitis patients due to the insufficient medical records, three IgA vasculitis patients due to no results of testing for ANCA at diagnosis and one IgA vasculitis patient due to a concomitant malignancy. Moreover, we further excluded two patients who fulfilled the EULAR/PRINTO/PRES criteria for IgA vasculitis and furthermore met the 2007 European Medicines Agency algorithm (the 2007 EMA algorithm) for AAV and classic polyarteritis nodosa (cPAN), in which authors added the modified contents of the 2012 CHCC definitions [7, 10]. Finally, we included 86 IgA vasculitis patients in this study.

Clinical and laboratory data at diagnosis and poor outcomes and medications during follow-up

As was described in Table 1, we obtained demographic, clinical and laboratory data at the time of diagnosis. Diabetes mellitus and hypertension at diagnosis of IgA vasculitis were counted as comorbidities. In this study, we reviewed the frequency of all-cause mortality, relapse, CKD (stage 3–5) and ESRD as poor outcomes of IgA vasculitis. All-cause mortality was defined as death for any reason during follow-up. Relapse was defined as a new development of

Table 1 Characteristics of 86 patients with IgA vasculitis at diagnosis and during follow-up

Variables	Values
Demographic data	
Age at diagnosis (year old)	36.0 (27.0)/36.2 ± 16.6
Male sex [N (%)]	37 (43.0)
ANCA positivity at diagnosis [N (%)]	
MPO-ANCA (or P-ANCA)	5 (5.8)
PR3-ANCA (or C-ANCA)	0 (0)
MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)	0 (0)
ANCA negative	81 (94.2)
Clinical manifestations at diagnosis [N (%)]	
Cutaneous	86 (100)
Arthritis	29 (33.7)
Gastrointestinal	38 (44.2)
Renal	50 (58.1)
Pulmonary	2 (2.3)
Nervous systemic	4 (4.7)
Laboratory results	
White blood cell count (/μL)	7875.0 (4192.5)/8627.7 ± 3875.2
Haemoglobin (g/dL)	13.5 (2.8)/13.0 ± 2.0
Platelet count (× 10^3/μL)	270.0 (106.5)/280.0 ± 1033.8
Immunoglobulin A (mg/dL)	308.0 (143.0)/374.8 ± 202.0
BUN (mg/dL)	12.8 (6.0)/16.7 ± 14. 9
Creatinine (mg/dL)	0.8 (0.3)/1.0 ± 0.8
Total protein (g/dL)	7.0 (0.8)/6.9 ± 1.0
Serum albumin (g/dL)	4.2 (0.8)/4.0 ± 0.7
AST (IU/L)	18.0 (8.0)/21.7 ± 11.1
ALT (IU/L)	16.0 (13.0)/21.8 ± 18.1
ESR (mm/h)	29.5 (29.3)/35.7 ± 30.1
CRP (mg/L)	2.7 (19.4)/17.2 ± 29.7
C3 (mg/dL)	112.2 (25.9)/116.0 ± 24.9
C4 (mg/dL)	25.2 (10.1)/27.0 ± 9.0
Urinalysis results at diagnosis [N (%)]	
Proteinuria	50 (58.1)
Haematuria	46 (53.5)
Follow-up duration (month)	38.5 (57.0)/53.0 ± 45.5
Comorbidities at diagnosis [N (%)]	
Diabetes mellitus	7 (8.1)
Hypertension	19 (22.1)
Poor outcomes during follow-up [N (%)]	
All-cause mortality	1 (1.2)
Relapse	12 (14.0)
Chronic kidney disease (stage 3–6)	13 (15.1)
End-stage kidney disease	5 (5.8)
Medications administered during follow-up [N (%)]	
Glucocorticoid	44 (51.2)
Cyclophosphamide	4 (4.7)
Azathioprine	6 (7.0)
Calcineurin inhibitor	5 (5.8)
Mycophenolate mofetil	4 (4.7)

Values are presented as a median (interquartile range, IQR)/mean ± standard deviation (SD) or number (percentage)

HSP Henoch-Schönlein purpura, *ANCA* antineutrophil cytoplasmic antibody, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *C3* complement 3, *C4* complement 4

symptoms of IgA vasculitis in a previously asymptomatic patient (at least for 1 month) [11]. CKD (stage 3–5) was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2, which was calculated by the equation proposed by Chronic Kidney Disease Epidemiology Collaboration (eGFR (CKD-EPI)) [12] and ESRD was defined as an impairment of renal function which requires dialysis. Thus, CKD (stage 3–5) included ESRD in this study. The follow-up duration was determined as the gap time from the diagnosis of AAV to the last visit. In patients with poor outcomes, the follow-up duration was defined as the gap time from the diagnosis of IgA vasculitis to death for the dead patients, to relapse for the patients with relapse, to the first notice of eGFR < 60 mL/min/1.73 m^2 to CKD (stage 3–5) patients and to the initiation of dialysis for the ESRD patients. Also, we counted the number of patients who received glucocorticoid, cyclophosphamide, azathioprine, calcineurin inhibitors and mycophenolate mofetil for the treatment of IgA vasculitis.

Histological assessment

We assessed the renal histological features based on the International Study of Kidney Disease in Children (ISKDC) classification and Oxford classification [13, 14]. We simplified the ISKDC classification into six grades as follows: minimal alterations (grade I), mesangial proliferation (grade II), mesangial proliferation or sclerosis with < 50% crescents (grade III), mesangial proliferation or sclerosis with 50–75% crescents (grade IV), mesangial proliferation or sclerosis > 75% crescents (grade V) and membranoproliferative-like glomerulonephritis (grade VI). We also used the Oxford classification as five simplified categories without subclasses such as mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis/adhesion, tubular atrophy/interstitial fibrosis and cellular/fibrocellular crescents.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median and interquartile range (IQR)/a mean ± standard deviation (SD) and categorical variables were expressed as number and the percentage. Significant differences in categorical variables between the two groups were analysed using the Chi square and Fisher's exact tests. Significant differences in continuous variables between the two groups were compared using the Mann–Whitney test. Comparison of cumulative survivals between the two groups was analysed by the Kaplan–Meier survival analysis. P values less than 0.05 were considered statistically significant.

Results

Characteristics of 86 patients with IgA vasculitis

The detection rate of ANCA in IgA vasculitis patients was 5.8% (5 of 86 patients) and all ANCAs were MPO-ANCA. Based on the EULAR/PRINTO/PRES criteria, cutaneous manifestation (purpura) was found in all patients and renal manifestation was the second common manifestation (58.1%), followed by gastrointestinal manifestation (44.2%) and arthritis/arthralgia (33.7%). The median serum IgA and C3 were 308.0 mg/dL and 112.2 mg/dL. Proteinuria and haematuria were detected in 58.1% and 53.5% of patients, respectively. Seven patients (8.1%) had diabetes mellitus and 19 (22.1%) hypertension at diagnosis. The median follow-up duration was 38.5 months. One patient died and 12 experienced relapse. Of 13 patients with CKD (stage 3–6), 5 patients had ESRD. The most commonly administered drug was glucocorticoid (51.2%), followed by azathioprine (7.0%) (Table 1).

Comparison of clinical and laboratory data

IgA vasculitis patients with ANCA were older than those without. Among clinical manifestations at diagnosis, patients with ANCA exhibited pulmonary (20.0% vs. 1.2%, $P = 0.007$) and nervous systemic manifestations (40.0% vs. 2.5%, $P < 0.001$) more frequently than those without. Among laboratory results, patients with ANCA exhibited the significantly higher median ESR (72.0 vs. 31.0 mm/h, $P = 0.007$) and CRP (8.8 vs. 2.6 mg/L, $P = 0.035$) than those without. However, there were no significant differences in comorbidities at diagnosis and poor outcomes and medications during follow-up between the two groups (Table 2).

Comparison of renal histological features

Fifty of the 86 patients exhibited renal manifestation, which was defined by the EULAR/PRINTO/PRES criteria, and 30 of the 50 patients with renal manifestation underwent a renal biopsy. For this reason, we could analyse the renal histological features only in these 30 patients. Two of 30 patients with renal histology had ANCA (6.7%). There were no significant differences in renal histological features based on both the ISKDC and Oxford criteria between IgA vasculitis patients with and without ANCA. Moreover, ANCA positivity did not affect CKD (stage 3–5) or ESRD occurrence (Table 3).

Table 2 Comparison of variables between IgA vasculitis patients with and without ANCA

Variables	IgA vasculitis patients without ANCA (N=81)	IgA vasculitis patients with ANCA (N=5)	P value
Demographic data			
Age at diagnosis (year old)	36.0 (27.0)/38.7 ± 16.3	63.0 (22.0)/58.2 ± 11.4	0.015
Male sex [N (%)]	35 (43.2)	2 (40.0)	0.888
Clinical manifestations at diagnosis [N (%)]			
Cutaneous	81 (100.0)	5 (100.0)	0.841
Arthritis	26 (32.1)	3 (60.0)	0.200
Gastrointestinal	36 (44.4)	2 (40.0)	0.846
Renal	46 (56.8)	4 (80.0)	0.307
Pulmonary	1 (1.2)	1 (20.0)	0.007
Nervous systemic	2 (2.5)	2 (40.0)	<0.001
Laboratory results at diagnosis			
White blood cell count (10^3/μL)	7760.0 (5040.0) /8598.2 ± 3707.9	9400.0 (NA) /9566.0 ± 1207.5	0.238
Haemoglobin (g/dL)	12.9 (2.5)/13.4 ± 1.9	10.0 (NA)/12.0 ± 2.2	0.172
Platelet count (10^5/μL)	260.0 (111.0)/277.2 ± 91.2	389.0 (NA)/351.0 ± 119.4	0.158
Immunoglobulin A (mg/dL)	304.0 (146.0)/355.4 ± 171.2	401.0 (NA)/456.0 ± 387.8	0.554
BUN (mg/dL)	12.7 (5.2)/15.3 ± 12.1	18.4 (NA)/21.5 ± 14.2	0.060
Creatinine (mg/dL)	0.8 (0.3)/0.9 ± 0.7	0.7 (NA)/0.8 ± 0.2	0.789
Total protein (g/dL)	7.0 (0.9)/6.9 ± 0.8	6.9 (NA)/7.1 ± 0.6	0.684
Serum albumin (g/dL)	4.2 (0.8)/4.1 ± 0.6	3.1 (NA)/3.5 ± 0.9	0.079
AST (IU/L)	19.0 (7.0)/20.4 ± 9.8	22.0 (NA)/33.6 ± 27.3	0.530
ALT (IU/L)	16.0 (13.0)/19.5 ± 14.1	17.0 (NA)/34.6 ± 43.5	0.919
ESR (mm/h)	31.0 (27.0)/33.8 ± 30.5	72.0 (NA)/88.0 ± 38.5	0.007
CRP (mg/L)	2.6 (18.9)/13.9 ± 23.5	8.8 (NA)/58.0 ± 61.9	0.035
C3 (mg/dL)	111.4 (27.0)/115.6 ± 23.1	119.6 (NA)/138.5 ± 41.8	0.160
C4 (mg/dL)	26.2 (10.1)/26.3 ± 8.5	25.8 (NA)/29.9 ± 9.7	0.426
Urinalysis results at diagnosis [N (%)]			
Proteinuria	46 (56.8)	4 (80.0)	0.307
Haematuria	44 (54.3)	2 (40.0)	0.533
Comorbidities at diagnosis [N (%)]			
Diabetes mellitus	6 (7.4)	1 (20.0)	0.318
Hypertension	17 (21.0)	2 (40.0)	0.320
Follow-up duration (month)	36.0 (58.0)/52.5 ± 45.1	57.0 (99.0)/59.8 ± 56.6	0.731
Poor outcomes during follow-up [N (%)]			
All-cause mortality	1 (1.2)	0 (0)	0.803
Relapse	11 (13.6)	1 (20.0)	0.688
Chronic kidney disease (stage 3–6)	13 (16.0)	0 (0)	0.331
End-stage kidney disease	5 (6.2)	0 (0)	0.567
Medications administered during follow-up [N (%)]			
Glucocorticoid	41 (50.6)	3 (60.0)	0.684
Cyclophosphamide	4 (4.9)	0 (0)	0.611
Azathioprine	6 (7.4)	0 (0)	0.528
Calcineurin inhibitor	5 (6.2)	0 (0)	0.567
Mycophenolate mofetil	4 (4.9)	0 (0)	0.611

Values are presented as a median (interquartile range, IQR)/mean ± standard deviation (SD) or number (percentage)

HSP Henoch-Schönlein purpura, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic, *BUN* blood urea nitrogen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *C3* complement 3, *C4* complement 4

Table 3 Comparison of renal histological features between IgA vasculitis patients with and without ANCA

Variables	IgA vasculitis patients without ANCA (N=28)	IgA vasculitis patients with ANCA (N=2)	P value
Demographic data			
Age at diagnosis (years old)	44.5 (29.0) /44.0 ± 17.3	68.0 (NA) /68.0 ± 2.8	0.081
Male gender [N (%)]	13 (46.4)	1 (50.0)	0.922
Renal involvement [N (%)]			
Renal manifestation [N (%)]	28 (100)	2 (100)	N/A
Proteinuria	20 (71.4)	1 (50.0)	0.523
Haematuria	28 (100)	2 (100)	N/A
Renal histology [N (%)]			
Immunoglobulin A deposits	28 (100)	2 (100)	N/A
C3 deposits	20 (71.4)	2 (100)	0.377
ISKDC classification			0.278
Class I	4 (14.3)	1 (50.0)	
Class II	6 (21.4)	0 (0)	
Class III	13 (46.4)	0 (0)	
Class IV	3 (10.7)	1 (50.0)	
Class V	2 (7.1)	0 (0)	
Class VI	0 (0)	0 (0)	
Oxford classification			
Mesangial hypercellularity	11 (39.3)	0 (0)	0.265
Endocapillary hypercellularity	9 (32.1)	1 (50.0)	0.605
Segmental glomerulosclerosis/adhesion	15 (53.6)	0 (0)	0.143
Tubular atrophy/interstitial fibrosis	3 (10.7)	0 (0)	0.626
Cellular/fibro-cellular crescents	13 (46.4)	1 (50.0)	0.922
Follow-up duration (months)	104.0 (94.0)	38.0 (NA)	0.212
Renal morbidities [N (%)]			0.201
Chronic kidney diseases (stage 3–5)	3 (10.7)	0 (0)	0.626
End-stage renal disease	2 (7.1)	0 (0)	0.696

Values are presented as a median (interquartile range, IQR)/mean ± standard deviation (SD) or number (percentage)

HSP Henoch-Schönlein purpura, *ANCA* antineutrophil cytoplasmic antibody, *C3* complement 3, *ISKDC* the International Study of Kidney Disease in Children

Comparison of the cumulative survival rates

The cumulative patients' survival rate and relapse-free survival rate did not seem to be affected by ANCA positivity at diagnosis in IgA vasculitis patients. Also, there were no significant differences in CKD (stage 3–5) and ESRD-free survival rates between IgA vasculitis patients with and without ANCA (Fig. 1).

Application of the classification criteria for AAV to IgA vasculitis patients with ANCA

Although at the entry of this study, we already excluded two patients with both IgA vasculitis and AAV, to reconfirm the classification of IgA vasculitis in patients with ANCA, we applied the 2007 EMA algorithm to five IgA vasculitis patients with ANCA. All patients with ANCA did not meet the 2007 EMA algorithm modified by the revised 2012

CHCC definitions for MPA, granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) at all [7, 10]. Two IgA vasculitis patients with ANCA underwent renal biopsy which revealed histological features compatible with IgA vasculitis nephritis. Thus, they could be distinguished from MPA, whereas three IgA vasculitis patients with ANCA did not undergo renal biopsy but two of them exhibited proteinuria without haematuria, which was compatible with the definition of renal involvement of IgA vasculitis based on the EULAR/PRINTO/PRES criteria. However, the 2007 EMA algorithm defines renal vasculitis as haematuria (RBC casts or > 10% RBC dysmorphism) or haematuria 2 + along with proteinuria 2 + on urine stick. These two patients showed no MPA-specific renal vasculitis and, thus, they could not be reclassified as MPA. The rest one patient without renal histology exhibited neither GPA surrogate marker nor evidence of renal vasculitis and, thus, could not be classified as MPA (Table 4).
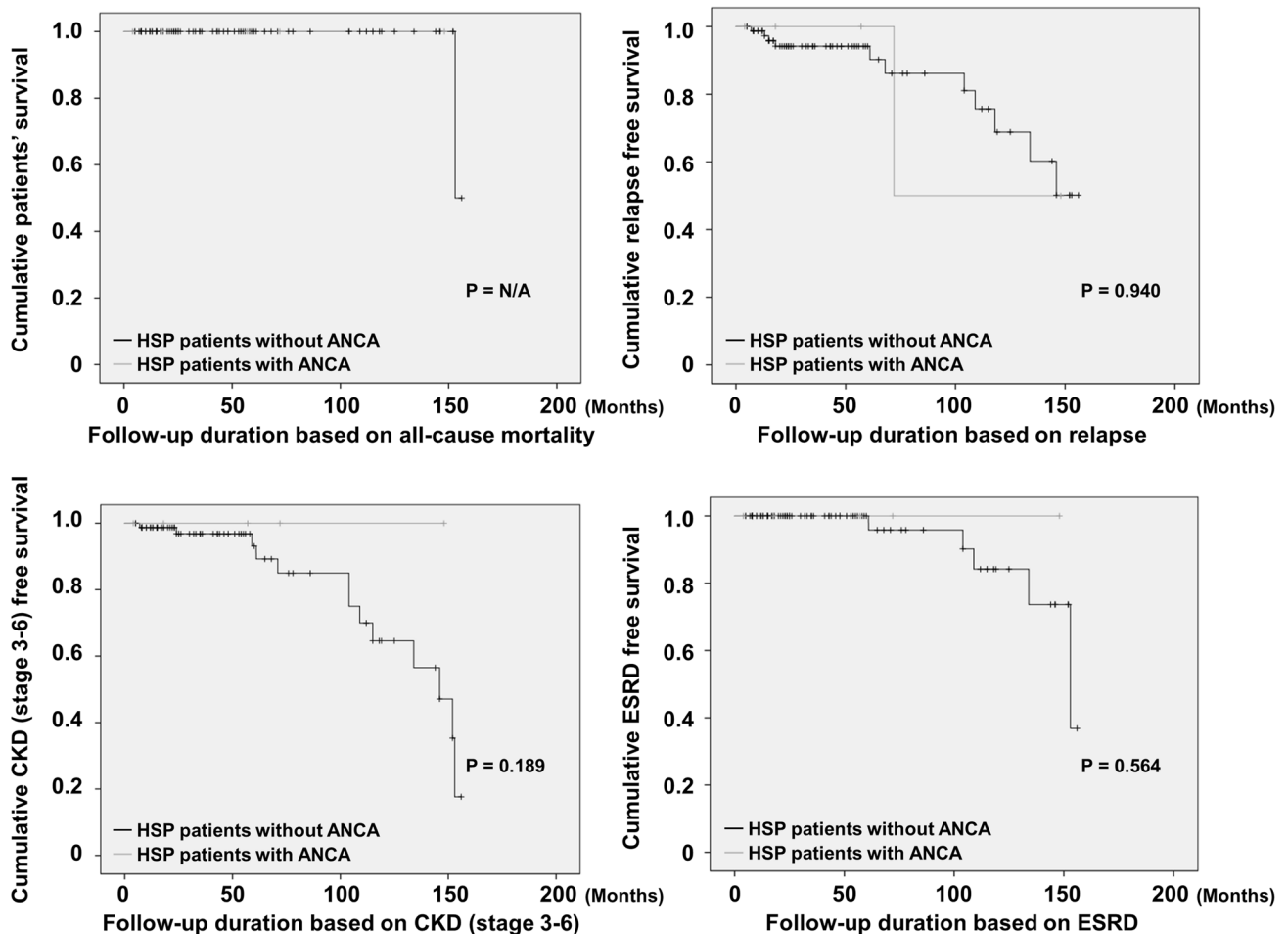
Fig. 1 Comparison of the cumulative survival rates of poor outcomes between IgA vasculitis patients with and without ANCA. There were no significant differences in all-cause mortality, relapse, CKD (stage 3–5) and ESRD-free survival rates between IgA vasculitis patients with and without ANCA. *ANCA* antineutrophil cytoplasmic antibody, *CKD* chronic kidney disease, *ESRD* end-stage renal disease

Discussion

In this study, we evaluated the frequency of ANCA detected at diagnosis and its clinical significance in 86 patients with IgA vasculitis during follow-up and found that 5.8% of IgA vasculitis patients had MPO-ANCA and poor outcomes of IgA vasculitis were not affected by the presence of ANCA. There have been several studies investigating the clinical implication of ANCA positivity in patients with IgA nephropathy, which is indistinguishable from glomerulonephritis of IgA vasculitis [7]. They reported that ANCA-positive IgA nephropathy exhibited more severe clinical and histological features but they suggested that not all ANCA play pathogenic roles in the pathogenesis of IgA nephropathy [15–17], whereas, in Korea, there have been only two case reports to date: one is regarding positive cytoplasmic (C)-ANCA in one of 30 Korean children patients with IgA vasculitis [18] and the other is a case of elderly onset IgA vasculitis with myeloperoxidase (MPO)-ANCA [19]. We

have reviewed the literature and could find two hypotheses on the production and detection of ANCA positivity in IgA vasculitis patients. Kim and Shin cited previous studies reporting an increase in TNF-alpha levels and a decrease in regulatory T cell population in IgA vasculitis patients. And they insisted that elevated serum TNF-alpha and deteriorated regulatory T cells might provoke pro-inflammatory cytokine storm, resulting in producing C-ANCA [18], whereas Ronda and colleagues demonstrated ANCA of IgA isotype in IgA vasculitis patients and suggest that the IgA ANCA target might be a membrane-associated protein rather than cytoplasmic protein and it might be different from the targets commonly recognised by IgG ANCA [20, 21]. Thus, we conclude that ANCA can be detected as a result of an inflammatory reaction of IgA vasculitis and, furthermore, it may be a pathogenic cause of IgA-related diseases.

In this study, ANCA subtype which was observed in five patients with IgA vasculitis was MPO-ANCA but not PR3-ANCA. In terms of renal vasculitis, MPO-ANCA is

primarily associated with necrotising crescentic glomerulonephritis of MPO-ANCA vasculitis but is rarely detected in IgA nephropathy. Ogawa and colleagues described the phenomenon of MPO-ANCA positivity in patients with IgA vasculitis (or IgA nephropathy) as the consequence of IgA-MPO-ANCA rather than the independent generation of MPO-ANCA [22]. Valenzuela and colleagues proposed a concept of microscopic polyangiitis and IgA vasculitis overlapping syndrome which is characterised by the synergistic effect of MPO-ANCA and IgA-containing immune complex [23]. Similarly, in our study, the frequencies of lung and neurological manifestations were significantly higher in IgA vasculitis patients with ANCA than those without (20.0% vs. 1.2%, $P = 0.007$ and 40.0% vs. 2.5%, $P < 0.001$). Given that central and peripheral nervous system dysfunction or pulmonary manifestation are known as very uncommon in IgA vasculitis patients [24, 25], we assume that ANCA might be involved in systemic symptoms other than those common in IgA vasculitis patients in the form of MPO-ANCA vasculitis rather than IgA-containing immune complex-induced vasculitis.

We have mentioned the possibility of MPA and IgA vasculitis overlapping syndrome in the process of explaining the association of MPO-ANCA (or MPO-ANCA IgA) with systemic manifestations. However, we applied the 2007 EMA algorithm for AAV and the 2012 CHCC definitions to all patients with IgA vasculitis and found that none fulfilled those criteria. In addition, we applied the ACR/EULAR 2017 provisional classification criteria for GPA to five patients with ANCA, which consist of nine items with different points. The total score of 5 or greater can classify a patient as GPA [26]. None of them could be classified as GPA by these criteria either. Thus, we conclude that the overlapping syndrome cannot explain ANCA positivity in IgA vasculitis in this study.

We intended to investigate poor outcomes, particularly renal failure, in IgA vasculitis patients; however, there are few previous studies on the effect of ANCA on renal function during the disease course of IgA vasculitis. Instead, given that IgA vasculitis is indistinguishable from IgA nephropathy as long as there are no extrarenal manifestations [7], we reviewed previous studies regarding the effect of ANCA on the deterioration in renal function in patients with IgA nephropathy. Huang and colleagues suggested that identifying and discerning between pathogenic and non-pathogenic ANCA should be required in patients with IgA nephropathy [15]. Yang and colleagues provide information on the renal pathogenic role of ANCA in IgA nephropathy by demonstrating that ANCA-positive patients with IgA nephropathy exhibited more severe and progressive renal and histological feature than ANCA-negative patients with IgA nephropathy. Furthermore, they suggested that immune complex containing IgA in ANCA-positive patients with IgA nephropathy

Table 4 Application of the 2007 EMA algorithm modified by the revised 2012 CHCC definitions to IgA vasculitis patients with ANCA

Patient's number	Conditions	ACR for EGPA (1990 ACR)	Histology compatible with 2012 CHCC definition for GPA	Histology compatible with 2012 CHCC definition for MPA and GPA surrogate markers	No histology and GPA surrogate markers and PR3- or MPO-ANCA positivity	Clinical and Histology compatible with 2012 CHCC definition for MPA and No GPA surrogate markers	No histology and No GPA surrogate markers and PR3- or MPO-ANCA positivity and renal vasculitis	Comment
	Classified as	EGPA	GPA	GPA	GPA	MPA	MPA	
1		No	No	No	No	No	No	Proteinuria without haematuria
2		No	No	No	No	No	No	Proteinuria without haematuria
3		No	No	No	No	No	Yes	Renal biopsy-proven HSP
4		No	No	No	No	No	Yes	Renal biopsy-proven HSP
5		No	No	No	No	No	No	No renal manifestation

Renal vasculitis: Haematuria (RBC casts or > 10% RBC dysmorphism) or haematuria 2+ & proteinuria 2+ on urine stick

EMA European medicine agency, *CHCC* Chapel Hill Consensus Conference, *HSP* Henoch-Schönlein purpura, *ANCA* antineutrophil cytoplasmic antibody, *ACR* the American College of Rheumatology, *EGPA* eosinophilic granulomatosis with polyangiitis, *GPA* granulomatosis with polyangiitis, *MPA* microscopic polyangiitis, *PR3* proteinase 3, *MPO* myeloperoxidase

might not be directly associated with ANCA production [16]. Meanwhile, Xie and colleagues focused on the presence of systemic (extrarenal) manifestations in ANCA-positive patients with IgA nephropathy [17]. Therefore, we conclude that ANCA could be considered a risk factor for the worsening of IgA nephropathy including IgA vasculitis nephritis despite the uncertain mechanism.

In this study, we assessed the detection rate and the subtype of ANCA and investigated the clinical significance of ANCA positivity at diagnosis in a considerable number of Korean adult patients with IgA vasculitis for the first time. Particularly, we unveiled that the effect of ANCA on the outcomes of IgA vasculitis was not clinically significant unlike previous studies in other countries [15–17]. However, our study has several issues. First, since our study is a monocentric retrospective study, the number of IgA vasculitis patients was not large enough to represent the clinical significance of ANCA in Korean patients with IgA vasculitis. For this reason, the simple comparison analysis of variables between IgA vasculitis patients with and without ANCA may have several limitations. And furthermore, in particular, the number of patients with biopsy results was too small to give forth the firmly more reliable data. However, as you know, so far, previous studies have reported the detection of ANCA in IgA vasculitis patients at a too low rate to conduct statistical analysis. Therefore, we believe that this study is meaningful as a pilot study to report the detection rate of ACA in a considerable number of patients with IgA vasculitis. Second, the follow-up duration was not long enough to reflect the outcomes of IgA vasculitis. Third, not all patients had undergone a renal biopsy. Future studies with a larger number of IgA vasculitis patients and a considerable follow-up period will provide clear information on the clinical significance of ANCA in Korean patients with IgA vasculitis.

In conclusion, 5 out of 86 patients with IgA vasculitis had ANCA but they did not fulfil the classification criteria for AAV at all. In addition, ANCA positivity tended to be clinically frequent in lung and neurological symptoms but did not seem to affect renal histology or overall prognosis in patient with IgA vasculitis. These results might be due to the results of excluding patients who met the classification criteria for AAV. Therefore, we suggest that in real clinical practice, physicians should first apply the classification criteria for AAV to patients with ANCA positivity and then, if not for AAV, apply the classification criteria for IgA vasculitis.

Author contributions All authors contributed to conception and design, or acquisition of data, or analysis and interpretation of data and participated in drafting the manuscript or revising it critically for important intellectual content. Also, all authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673).

Informed consent The patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

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