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ANCA positivity at the time of renal biopsy is associated with chronicity index of lupus nephritis

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Abstract

We investigated the association of antineutrophil cytoplasmic antibody (ANCA) positivity with lupus nephritis (LN) activity, histological features and prognosis in Korean patients with biopsy-proven LN having the results of both myeloperoxidase (MPO–ANCA) and proteinase 3 (PR3)–ANCA. We retrospectively reviewed the medical records of 91 LN patients having the results of ANCA. We divided patients with LN into the two groups according to the ANCA positivity. We collected clinical and laboratory data at kidney biopsy and histological features such as LN class including class I, II, III, IV-S, IV-G and V, and activity and chronicity index. We evaluated prognosis of LN during the follow-up by death and kidney failure. Twelve of 91 patients (13.2%) had ANCA at kidney biopsy. There were no differences in demographic data, comorbidities, reasons for kidney biopsy and laboratory data at kidney biopsy between patients with and without ANCA. In 12 LN patients with ANCA, Class III was the most frequently observed LN class (41.7%), while in 79 LN patients without ANCA, class IV-G was the most often detected LN class (35.4%). There were no meaningful differences in classes of LN between the two groups. On the other hand, patients with ANCA exhibited the higher median chronicity index than those without (2.5 vs. 1.0, $P=0.028$), unlike activity index. ANCA positivity exhibited no association with death or kidney failure during the follow-up. ANCA positivity at kidney biopsy is associated with chronicity index of LN.

Keywords Systemic lupus erythematosus · Lupus nephritis · Antineutrophil cytoplasmic antibody · Histology · Prognosis

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, which is characterised by various symptoms and signs depending on the involved organs [1]. Lupus nephritis (LN) is one of the serious phenotypes of SLE, which is provoked by the immune-complex deposition in glomeruli of kidneys and lead to glomerular capillary damages along with membranous nephropathy and mesangial proliferation [2]. LN is categorised into six classes from class I to class IV, based on histopathological patterns and class IV is further divided into two subclasses according to the extent of involvement of diffuse proliferative LN such as class IV-S (less than 50% of glomerulus) and class IV-G (more than 50% of glomerulus) [3]. Proliferative LNs including class III and class IV often exhibit a worse prognosis and in general, require glucocorticoid and immunosuppressive drugs as the induction therapy [4]. Nevertheless, end-stage renal diseases (ESRD) is observed in up to 30% of patients with proliferative LN [5]. On the other hand, class V LN typically exhibits a slower and progression, so approximately

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10% of patients have ESRD in 10 years. When proliferative LN coexists, the induction therapy for class V LN is similar to class III and IV LN, whereas, non-nephrotic class V LN often require angiotensin-converting enzyme inhibitor or angiotensin receptor blocker as the first drug [4].

Antineutrophil cytoplasmic antibody (ANCA) is a group of autoantibodies recognising typical antigens in the cytoplasm of neutrophils, mainly myeloperoxidase (MPO) and proteinase 3 (PR3). In healthy individuals, ANCA can be detected and it is called non-pathogenic ANCA or natural ANCA [6]. However, when this regulation is broken, ANCA initiates pathogenic autoimmunity and induces ANCA-associated vasculitis (AAV) [7]. ANCA was reported to be detected in patients with LN more frequently than general population and, furthermore, it was associated with diffuse proliferative LN, particularly class IV-S rather than class IV-G [8, 9]. However, the association between ANCA positivity and LN activity, histological features or prognosis still remains debating [9–11]. Furthermore, when MPO–ANCA or PR3–ANCA is detected, the possibility that ANCA-associated necrotizing and crescentic glomerulonephritis may overlap with LN should not be ignored [12]. However, there was no report regarding the effect of ANCA positivity on LN activity, histological features and prognosis in Korean patients with LN. Considering the ethnic difference in responses to immunosuppressive treatment [13], investigating the clinical implication of ANCA positivity in patients with LN may be valuable. Hence, in this study, we included 91 Korean patients with biopsy-proven LN having the results of MPO–ANCA and PR3–ANCA at kidney biopsy. And we investigated the association of ANCA positivity with LN activity, histological features and prognosis in LN patients in a single centre.

Methods

Patients

We retrospectively reviewed the electrical medical records of 91 patients with LN according to the inclusion criteria as follows: (i) patients with LN who had been first classified as SLE at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; (ii) those who met the American College of Rheumatology revised criteria for the classification of SLE [14]; (iii) those who underwent kidney biopsy and in whom the classification of LN was done based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN [3, 15]; (iv) those who had the results of MPO–ANCA and PR3–ANCA. ANCA tests were not routinely performed in SLE patients. However, they were usually performed, when lupus nephritis was suspected and other renal vasculitides should be excluded. This study was approved by the institutional Review Board of Severance Hospital (4-2017-0444).

Clinical and laboratory data

We first searched ANCA (MPO–ANCA and PR3–ANCA) positivity. MPO–ANCA and PR3–ANCA had been measured by enzyme-linked immunosorbent assay (ELISA) kit for anti-PR3 and anti-MPO (Inova Diagnostics, San Diego, USA) in 53 LN patients before 2013, and by the novel anchor-coated highly sensitive (hs) Phadia ELiA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) using human native antigens, performed on a Phadia250 analyser in 38 LN patients after 2013. We divided 91 patients with LN into the two groups according to the ANCA positivity and 12 patients were belonging to the group of 'patients with ANCA'. We collected age at biopsy, gender, the time-gap from diagnosis of SLE to kidney biopsy and the follow-up duration. Due to lack of information of the initial clinical events compatible with the indication of kidney biopsy in patients with LN, we could collect only the time-gap from SLE diagnosis to kidney biopsy. The follow-up duration was defined as either the period from diagnosis of SLE to the last visit for survived patients or the period from diagnosis of SLE to the time of death for deceased patients or the initiation of dialysis for ESRD patients. We also assessed comorbidities which can affect kidney histology such as diabetes mellitus and hypertension. We investigated reasons for kidney biopsy such as proteinuria, hematuria and creatinine elevation. We also collected the amount of proteinuria for 24 h, creatinine level, anti-ds DNA titre and complement 4 level as laboratory results for LN activity at kidney biopsy.

Histological features

We reviewed the histological classification of LN based on (ISN/RPS) 2003 classification of LN [3, 15]. Therefore, we counted the number of LN patients belonging to six categories including class I, II, III, IV-S, IV-G and V. Furthermore, we obtained the reporting comments regarding the activity index and chronicity index. National institutes of health scoring systemic for histologic features of renal biopsy are described in Supplementary Table 1 [16]. Crescent formation, which is a histological feature of AAV, was found in 17 patients and was evenly observed in the two groups based on ANCA positivity, MPO–ANCA positivity and each class of LN (Supplementary Table 2).

Prognosis

We evaluated prognosis of LN during follow-up by the two parameters of death and kidney failure. Death

was defined only when it was associated with SLE or immunosuppressive drugs for SLE. Three patients were excluded due to cancer-related death. Kidney failure was defined as a status which needs dialysis therapy.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (interquartile range, IQR) and categorical variables were done 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. Cumulative patient and kidney survival rates were analysed by the Kaplan–Meier survival analysis. *P* values less than 0.05 were considered statistically significant.

Results

Comparison of baseline characteristics between LN patients with and without ANCA at the time of kidney biopsy

The comparison of baseline characteristics between LN patients with and without ANCA at kidney biopsy is shown in Table 1. Twelve of 91 patients (13.2%) had ANCA at the time of kidney biopsy and among 12 patients with ANCA, 11 patients had MPO–ANCA and only one patient had PR3-ANCA. In terms of demographic data, age at kidney biopsy, male gender, time-gap from diagnosis of SLE to kidney biopsy and the follow-up duration did not differ between patients with and without ANCA. The frequencies of diabetes mellitus and hypertension were similar between the two groups. All patients underwent kidney biopsy due to proteinuria. The frequencies of haematuria and creatinine elevation as reasons for kidney biopsy did not differ between the two groups. The differences in the median amount of proteinuria per 24 h and creatinine level were not remarkable between patients with and without ANCA (2.0 vs. 2.1 g, $P=0.106$ and 1.0 vs. 0.8 mg/dL, $P=0.214$). There were no

Table 1 Comparison of baseline characteristics between LN patients with and without ANCA at the time of kidney biopsy

Variables	Patients with ANCA ($N=12$)	Patients without ANCA ($N=79$)	*P* value
ANCA type			
MPO–ANCA	11 (91.7)	0 (0)	N/A
PR3–ANCA	1 (8.3)	0 (0)	N/A
Demographic data			
Age at kidney biopsy (year)	39.0 (15.0; 63.0)	34.0 (10.0; 63.0)	0.515
Male gender [*N*, (%)]	1 (8.3)	10 (12.7)	0.668
Time-gap from diagnosis of SLE to kidney biopsy (months)	0 (0; 142.0)	7.0 (0; 231.0)	0.304
Follow-up duration (years)	7.9 (0.5; 16.8)	7.4 (0; 24.8)	0.973
Comorbidities at kidney biopsy			
Diabetes mellitus	1 (8.3)	6 (7.6)	0.929
Hypertension	3 (25.0)	19 (24.1)	0.943
Reason for kidney biopsy			
Proteinuria	12 (100)	79 (100)	1.000
Haematuria	8 (66.7)	43 (54.4)	0.426
Creatinine elevation	4 (33.3)	14 (17.7)	0.206
Laboratory results at kidney biopsy			
Proteinuria/24 h (g)	2.0 (0.4; 5.6)	2.1 (0.1; 12.3)	0.106
Creatinine (mg/dL)	1.0 (0.5; 2.8)	0.8 (0.4; 4.4)	0.214
Anti-ds DNA (IU/mL)	0 (0; 677.5)	31.0 (0; 706.2)	0.097
Complement 4 (mg/dL)	3.2 (0; 31.6)	5.5 (0; 34.5)	0.856

Values are expressed as median (minimum; maximum) and number (%)

LN lupus nephritis, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic

significant differences in the concentrations of anti-ds DNA titre and complements between the two groups.

Histological features of kidney

In 12 LN patients with ANCA, class III was the most frequent (41.7%), followed by class IV-G (33.3%), class IV-S (16.7%) and class V (8.3%). By contrast, in 79 LN patients without ANCA, class IV-G was the most often detected (35.4%). Class I was found in 5 patients (6.3%), class II in 6 patients (7.6%), class III in 21 patients (26.6%), class IV-S in 6 patients (7.6%) and class V in 13 patients (16.5%). There were no significant differences in classes of LN between patients with and without ANCA (Table 2). On the other hand, the median activity index did not differ between the two groups. However, patients with ANCA exhibited the higher median chronicity index than those without (2.5 vs. 1.0, $P = 0.028$) (Table 2). We also compared the chronicity between 11 patients with MPO–ANCA and 80 those without. Patients with MPO–ANCA also exhibited the increased chronicity index compared to those without (3.0 vs. 1.0, $P = 0.033$) (Table 2).

Table 2 Histologic features of kidney

Variables	Patients with ANCA ($N = 12$)	Patients without ANCA ($N = 79$)	P value
Class of LN [N, (%)]			
I	0 (0)	5 (6.3)	0.370
II	0 (0)	6 (7.6)	0.323
III	5 (41.7)	21 (26.6)	0.281
IV-S	2 (16.7)	6 (7.6)	0.301
IV-G	4 (33.3)	28 (35.4)	0.887
V	1 (8.3)	13 (16.5)	0.467
Index			
Activity index	7.5 (3.0; 21.0)	7.0 (0; 21.0)	0.237
Chronicity index	2.5 (0; 8.0)	1.0 (0; 9.0)	0.028
Variables	Patients with MPO–ANCA ($N = 11$)	Patients without MPO–ANCA ($N = 80$)	P value
Index			
Activity index	7.0 (3.0; 13.0)	6.5 (0; 21.0)	0.571
Chronicity index	3.0 (0; 8.0)	1.0 (0; 9.0)	0.033

Values are expressed as median (minimum; maximum) and number (%)

ANCA antineutrophil cytoplasmic antibody, *LN* lupus nephritis

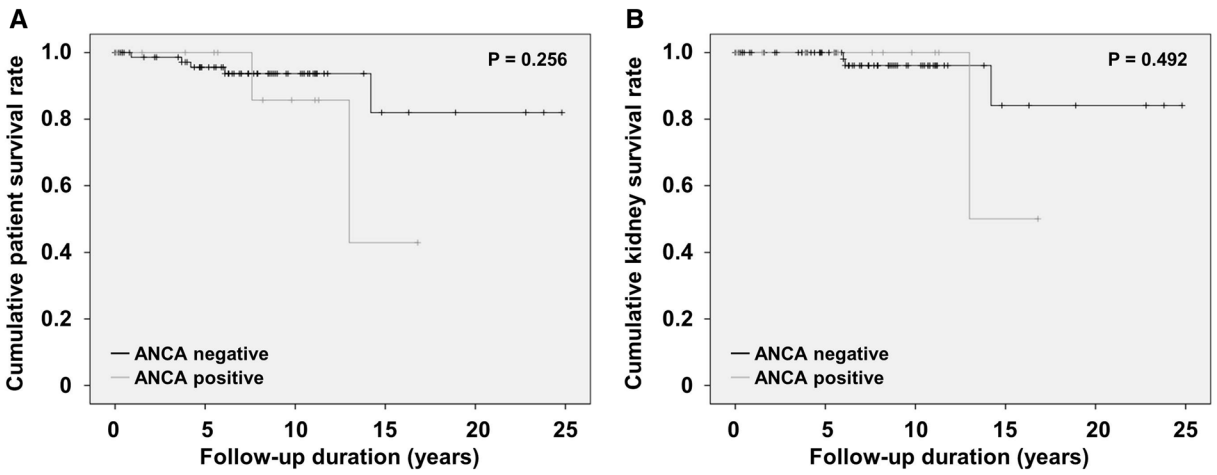

Fig. 1 Cumulative patient and kidney survival rates. Antineutrophil cytoplasmic antibody (ANCA) positivity was not association with cumulative patient and kidney survival rates in patients with lupus nephritis during follow-up

Cumulative patient and kidney survival rates

ANCA positivity influenced neither death nor kidney failure in LN patients during follow-up (Fig. 1).

Discussion

In this study, we found that patients with ANCA had the higher chronicity index than those without. However, ANCA positivity was not associated with poor outcome of LN. Thus, we conclude that ANCA positivity at kidney biopsy was meaningfully associated with only the chronicity index.

A kidney biopsy is usually performed when LN exhibits clinically meaningful aggravation which requires histological classification for the proper induction therapeutic regimens. Thus, in this clinical situation, the activity index of LN may be similarly increased in both patients with and without ANCA regardless of the detailed items of the activity index. However, the chronicity index may be affected by various factors including comorbidities during a relatively long time-gap from diagnosis of SLE to kidney biopsy. A previous study reported that ANCA might be associated with the higher chronicity index in LN patients [17]. This report supports our conclusion that ANCA positivity contributes to the chronicity index of LN. Furthermore, when we compared the chronicity index between 11 patients with MPO–ANCA and 80 those without MPO–ANCA, the results were similar to the comparison analysis between patients with and without overall ANCA. This finding implies that MPO–ANCA mainly contributed to the chronicity index of LN.

The histological features of kidney in patients with ANCA-associated renal vasculitis are mainly characterised by pauci-immune glomerular inflammation. The most common finding is known as crescentic necrotising glomerulonephritis, followed by crescentic glomerulonephritis and diffuse global glomerulosclerosis in accordance with Berden's AAV classification [18]. Furthermore, both cellular and fibrous crescents are also detected in kidney-tissues of ANCA-associated renal vasculitis [18, 19]. Here, glomerulosclerosis and fibrous crescents are belonging to the detailed items of the chronicity index. Thus, it is reasonably speculated that the potential of preceding ANCA-associated renal vasculitis might increase the chronicity index of LN in patients with ANCA. However, we reclassified 12 LN patients with ANCA based on the American College of Rheumatology 1990 criteria, the 2007 European Medicines Agency algorithm and 2012 revised Chapel Hill Consensus Conferences Nomenclature of Vasculitides but we found no patients reclassified as AAV [20–22]. Furthermore, the frequency of the crescent formation, which is a typical feature of AAV, was evenly observed in the two groups based on ANCA positivity, particularly MPO–ANCA positivity.

There are two important supporting evidences. First, the time-gap from diagnosis of SLE to kidney biopsy in patients without ANCA was longer than those with. Nonetheless, despite the longer time-gap from diagnosis to LN occurrence in patients without ANCA, the finding that the chronicity index of patients with ANCA was higher than those without ANCA suggests that ANCA might be involved in the pathogenesis of LN and accelerate chronic inflammation in kidneys. Second, patients with ANCA exhibited the lower median anti-ds DNA titre and the higher median complement 4 level than those without. This means that inflammation might have preceded the time of kidney biopsy and there might be subclinical glomerular inflammation before LN development.

It has been reported that class IV-S of LN is associated with ANCA positivity in that segmental crescentic formation of class IV-S LN is similar to AAV and ANCA test was performed more frequently in patients exhibiting AAV features [7, 8]. In our study, class IV-S was histologically confirmed in patients with ANCA more than two times as often as those without, but it was not significant (16.7% vs. 7.6%, $P = 0.301$).

It is still controversial that ANCA is associated with poor prognosis of LN such as death and renal failure [8, 9]. As a limitation of our study, we did not serially measure ANCAs till the time of death and renal failure. However, considering the possibility of seronegative or seropositive conversion due to a fluctuation in its serum titre [23], ANCAs at the time of kidney biopsy cannot directly influence on cumulative patient or kidney survival rates. Therefore, we could not clarify the association between ANCA positivity and prognosis of LN in this study.

Our study has a strong advantage. We first assessed whether ANCA positivity at kidney biopsy can be associated with the activity index and chronicity index of LN, and finally demonstrated the association of ANCA positivity and the chronicity index. However, our study also has several issues: first, the number of patients was not large enough to conduct the multivariable analysis or represent all Korean patients with LN. Second, two different detection methods for ANCA positivity due to a retrospective study may be a potential technical limitation, although the agreement rate of the former and latter methods was fully verified at the time of device replacement. Third, since this study was retrospectively designed, serial clinical and laboratory data-related LN activity in ANCA-positive patients with LN were not available. And we could not calculate systemic damage indices in all patients in this study either. If future studies can prospectively monitor LN activity and measure ANCA serially, they could reveal dynamic information regarding the effect of ANCA positivity on LN during follow-up. In conclusion, although this study is a retrospective pilot study, we provide a valuable

possibility that ANCA information at kidney biopsy is associated with the chronicity index of LN.

Author contributions JYP and S-WL collected the data and analysed the results and wrote the manuscript, under the guidance of SMJ and JJS; Y-BP contributed to writing and critically reviewed the manuscript; JYP and SWL designed, analysed the results, critically reviewed the manuscript and wrote the final version. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional Review Board of Severance Hospital (4-2017-0444).

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

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