International Journal of General Medicine

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SHORT REPORT

Anticardiolipin Antibody Plays a More Important Role Than Anti-β2-Glycoprotein I Antibody in Activating Complement in Patients with Lupus Nephritis

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Objective: This research aimed to explore the correlation between antiphospholipid antibodies (aPLs) and complement activation in lupus nephritis (LN) patients.

Methods: A retrospective analysis was carried out on patients diagnosed with LN based on renal biopsy from June 2019 to June 2022. The study assessed levels of IgM, IgA, and IgG subtypes of anticardiolipin antibodies (aCLs) and anti-β2-glycoprotein I (anti-β2-GPI) antibodies. Pathological and clinical data were collected concurrently with the renal biopsy.

Results: The analysis included 76 LN patients, with 44.7% testing positive for aPLs. LN patients with positive aPLs exhibited increased hematuria, higher SLEDAI scores, reduced serum C3 and C4 levels, and more C1q deposits in the glomerulus compared to those with negative aPLs ($P<0.05$). Correlation analysis demonstrated the inverse relationships between IgG-aCL levels and serum C3 and C4 levels (r=−0.29, $P=0.005$; r=−0.24, $P=0.016$, respectively), as well as a positive correlation with C4 deposits in the glomerulus (r=0.20, $P=0.041$).

Conclusion: This investigation suggests that aPLs, particularly IgG-aCLs, may be associated with the severity of LN and could contribute to the activation of classical complement pathways.

Keywords: anticardiolipin antibodies, aCLs, anti-β2GPI antibodies, complement activation, lupus nephritis, LN

Introduction

Antiphospholipid antibodies (aPLs) encompass a diverse group of antibodies targeting phospholipids or phospholipid-binding proteins. Notable members include anticardiolipin antibodies (aCLs) and anti-β2-glycoprotein I (anti-β2GPI) antibodies.[1] First identified in the early 1900s, anticardiolipin antibodies target cardiolipin, a phospholipid found in cell membranes. Conversely, anti-β2GPI antibodies, discovered in the 1990s, target β2GPI, a cardiolipin binding protein. aPLs have been strongly linked to the occurrence of thrombosis and pregnancy-related complications in antiphospholipid syndrome (APS).[1]

APS can manifest as a standalone primary syndrome or as a secondary condition accompanying an underlying disease, most commonly systemic lupus erythematosus (SLE).[2] Approximately 30–40% of SLE patients harbor aPLs, putting them at an elevated risk of thrombotic events, pregnancy-related issues, thrombocytopenia, pulmonary hypertension, valvular disease, and renal complications compared to SLE patients without aPLs.[3,4] The pathogenic mechanisms through which aPLs contribute to organ damage involve disturbances in anticoagulant and fibrinolytic systems, inflammation, and activation of the complement system.[5] In 2012, anti-β2GPI antibodies were included in the new antiphospholipid antibody criterion of SLE.[6] Mehrani et al found IgG-anti-β2GPI had the strongest association with thrombosis in SLE while IgA-anti-β2GPI was more strongly associated with deep venous thrombosis and with stroke.[7]

While prior studies have demonstrated the association between aPLs and a high risk of renal complications in SLE patients, the specific association between aPLs and complement activation in those with SLE or lupus nephritis (LN) remains

Received: 12 November 2023
Accepted: 4 February 2024
Published: 9 February 2024

insufficiently explored. This retrospective study aims to address three key objectives: 1) determine the prevalence of various aPL subtypes in LN patients, including IgM, IgA, and IgG subtypes of aCLs, and anti-β2-GPI antibodies, 2) examine the clinical and pathological correlations of aPLs, and 3) investigate the association between aPLs and complement activation.

Subject Recruitment

In this retrospective investigation, individuals admitted to Qianjiang Central Hospital from June 2019 to June 2022 were selectively included. Eligible patients met the criteria for SLE as revised by the American Rheumatism Association in 1997[8] and exhibited clinical manifestations of LN. Renal biopsies were performed upon hospitalization for all participants. The local ethics committee of the Qianjiang Central Hospital approved the study protocol (Approval Number: 202203). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all patients. Demographic information and laboratory analysis were collected from medical records. We confirmed that all the data was anonymized and maintained with confidentiality.

Data Collection

Prior to renal biopsy, demographic details, SLE disease activity index (SLEDAI), nephropathy duration, hematuria, urine protein/creatinine ratio, serum creatinine, serum albumin, estimated glomerular filtration rate (eGFR), serum hemoglobin (Hb), white blood cell (WBC) and platelet counts, serum C3 and C4, anti-dsDNA, IgM, IgA, and IgG aCLs, anti-β2-glycoprotein I antibodies, and thrombotic or pregnancy morbidity events were acquired for each patient.

Laboratory Assessments

IgM, IgA, and IgG aCLs, as well as anti-β2GPI antibodies, were quantified using ELISA kits from EUROIMMUN-Medizinische -Labordiagnostika-AG, Lübeck, Germany. Positivity criteria were defined as values exceeding 20 U/mL for IgA or IgG isotypes and 15 U/mL for IgM isotype for aCLs, while values exceeding 18 U/mL were deemed positive for anti-β2GPI antibodies (IgM, IgA, or IgG isotype). Complement components C3 and C4 were assessed through a nephelometric approach.

Histopathological Analysis

Renal tissues from biopsies were processed, stained with various techniques, and analyzed in accordance with the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification[9] of LN by a dedicated pathologist. Parameters including chronicity index, activity index, mesangial proliferation, classification, membrane thickness, endothelial proliferation, micro-thrombus, crescent, loops necrosis, and the chronic renal tubular interstitial inflammation ratio were documented. The intensities of glomerular immunofluorescence staining were semi-quantitatively scored as follows: 0, 1, 2 and 3 indicate no, mild, moderate and intense glomerular staining, respectively.[10]

Statistical Methods

Descriptive statistics were employed, presenting variables as means with standard deviations or proportions. Chi-square test or *t*-test compared differences between LN groups with/without aPLs. Spearman's or Pearson's correlation tests assessed associations between aPL levels, serum complement levels, and kidney complement deposits. Binary logistic regression determined independent variables associated with aPL presence. A significance threshold of $P<0.05$ was utilized, and all tests were executed using SPSS 22 (IBM, USA).

Results

In total, 76 LN patients who met inclusion criteria were recruited into this research. Among these LN patients, 34 (44.7%) exhibited the presence of aPLs (Table 1). The positivity rates for aCLs and anti-β2GPI antibodies were 34.2% and 22.3%, respectively.

Table 2 compares the clinical disparities between LN groups with/without aPLs. LN patients with positive aPLs demonstrated higher instances of hematuria ($P=0.035$), elevated SLEDAI ($P=0.019$), decreased Hb ($P=0.019$), reduced WBC ($P=0.002$), and lower serum C3 ($P=0.002$) and C4 ($P=0.016$) compared to their counterparts with negative aPLs.

Table 1 Classification of aPLs-Positive Patients

aPLs Assays	Positive Patients (n)	Positive Patients (%)
aCL or anti-β2GPI	34	44.7
aCL	26	34.2
IgG-aCL	15	19.7
IgM-aCL	13	17.1
IgA-aCL	5	6.5
anti-β2GPI	17	22.3
IgG-anti-β2-GPI	7	9.2
IgM-anti-β2-GPI	3	3.9
IgA-anti-β2-GPI	9	11.8

Abbreviations: aPLs, antiphospholipid antibodies; aCL, anticardiolipin.

Table 2 Clinical Data of LN Patients with or Without Positive aPLs

Variables	aPLs(+) group(n=34)	aPLs(-) group(n=42)	*P* value
Male (n, %)	6(17.6)	11(26.1)	0.419
Age (years)	32.3±14.8	33.2±13.5	0.783
LN duration(months)	4.8(0.3–72)	7.9(0.2–72)	0.506
Urine P/C ratio (g/g)	3.1±2.2	3.4±2.5	0.628
Hematuria positivity (n, %)	26(76.4)	22(52.3)	0.035*
Hb (g/dl)	90.2±24.5	104.9±28.0	0.019*
WBC(10^9/l)	4.4±2.2	6.5±3.2	0.002*
PLT(10^9/l)	159.5±61.0	177.9±71.4	0.240
Albumin(g/l)	26.0±6.8	27.2±7.8	0.497
Serum creatinine (μmol/l)	92.3±35.2	87.4±34.7	0.213
eGFR(mL/min/1.73m^2)	75.6±37.6	86.5±38.2	0.219
Anti-dsDNA (n, %)	29(85.2)	34(80.9)	0.762
SLEDAI	11.3±3.2	9.3±3.8	0.019*
Cutaneous disorder (n, %)	6(17.6)	7(16.6)	1.000
Arthritis (n, %)	8(23.5)	10(23.8)	1.000
Serositis (n, %)	10(29.4)	9(21.4)	0.439
Neurologic disorder (n, %)	2(5.8)	1(2.3)	0.584
Serum C3(mg/dl)	37.0±16.6	56.7±32.7	0.002*
Serum C4(mg/dl)	5.8±5.1	11.3±12.1	0.016*
Thrombotic events (n, %)	2(5.8)	1(2.3)	0.584
Pregnancy morbidity events (n, %)	2(5.8)	1(2.3)	0.584

Notes: Data are shown as mean± SD (standard deviation) or percentages. *$p< 0.05$.
Abbreviations: LN, lupus nephritis; aPLs, antiphospholipid antibodies; P/C, protein to creatinine; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; eGFR, estimated glomerular filtration rate; SLEDAI, systemic lupus erythematosus (SLE) disease activity index.

Nevertheless, there were no obvious differences in sex, age, disease duration, eGFR, urine protein/creatinine ratio, and other clinical parameters between the two groups.

Table 3 demonstrates the renal pathological variances between LN groups with/without aPLs. LN patients with positive aPLs exhibited a higher presence of C1q deposits in the glomerulus compared to those with negative aPLs (P=0.037). However, there were no distinctions in activity index, chronicity index, ISN/RPS classification, crescent, C3 and C4 deposits, and other pathological data between the two groups.

To identify the predominant subtypes influencing complement activation, particularly in glomerular deposits, correlation analysis was conducted between various aPL subtypes and complement components (Table 4). The level of IgG-aCLs displayed a negative association with serum C3 and C4 levels (r=−0.29, P=0.005; r=−0.24, P=0.016, respectively), and

Table 3 Pathological Data of LN Patients with or Without aPLs

Variables	aPLs(+) group (n=34)	aPLs(-) group (n=42)	P value
Activity index	2.7±2.4	2.4±1.9	0.512
Chronicity index	2.0±1.5	2.4±2.0	0.372
ISN/RPS classification			0.891
II (n, %)	3(8.8)	3(7.1)	
III (n, %)	7(20.5)	7(16.6)	
IV (n, %)	19(55.8)	20(47.6)	
V (n, %)	11(32.3)	13(30.9)	
VI (n, %)	0(0.0)	1(2.3)	
Mesangial proliferation			0.650
Mild (n, %)	20(58.8)	29(69.0)	
Moderate (n, %)	13(38.2)	12(28.5)	
Severe (n, %)	1(2.9)	1(2.3)	
Endothelial proliferation (n, %)	15(44.1)	16(38.0)	0.644
Crescent (n, %)	13(38.2)	19(45.2)	0.642
Cellular crescent (n, %)	2(5.8)	9(21.4)	0.098
Fibrous crescent (n, %)	1(2.9)	2(4.7)	1.000
Hybrid crescent (n, %)	3(8.8)	4(9.5)	1.000
Segmental crescent (n, %)	14(41.1)	18(42.8)	1.000
Loops necrosis (n, %)	2(5.8)	1(2.3)	0.584
Micro-thrombosis(n, %)	3(8.8)	1(2.3)	0.319
Ratio of chronic renal tubular interstitial inflammation (%)	11.3±8.4	17.6±14.3	0.188
IgG deposition (n, %)	28(82.3)	28(66.6)	0.190
IgA deposition (n, %)	26(76.4)	31(73.8)	1.000
IgM deposition(n, %)	32(94.1)	36(85.7)	0.285
C3 deposition (n, %)	33(97.0)	35(83.3)	0.068
C4 deposition (n, %)	23(67.6)	23(54.7)	0.346
C1q deposition (n, %)	33(97.0)	34(80.9)	0.037*

Notes: Data are shown as mean± SD (standard deviation) or percentages. *$p<0.05$.
Abbreviations: LN, lupus nephritis; aPLs, antiphospholipid antibodies; ISN/RPS, WHO: renal biopsy findings according to the International Society of Nephrology/Renal Pathology Society.

Table 4 Correlation Between Complement Components and Different Subtypes of aPLs in Patients with LN

Variables	IgG-aCL		IgM-aCL		IgA-aCL		IgG-anti-β2-GPI		IgM-anti-β2-GPI		IgA-anti-β2-GPI	
	r value	p value	r value	p value	r value	p value	r value	p value	r value	p value	r value	p value
Serum C3	−0.29	0.005*	−0.19	0.043*	−0.06	0.290	−0.12	0.155	−0.09	0.218	−0.02	0.434
Serum C4	−0.24	0.016*	−0.21	0.036*	−0.09	0.202	−0.18	0.060	−0.02	0.408	−0.06	0.288
C3deposition	0.02	0.427	−0.05	0.321	−0.09	0.222	0.08	0.245	−0.01	0.439	0.06	0.300
C4 deposition	0.20	0.041*	−0.11	0.170	0.02	0.424	0.01	0.448	0.13	0.124	0.16	0.081
C1q deposition	0.01	0.446	−0.11	0.172	0.12	0.142	0.09	0.207	0.07	0.266	0.20	0.180

Note: *p< 0.05.
Abbreviations: LLN, lupus nephritis; aPLs, antiphospholipid antibodies; aCL, anticardiolipin; r, correlation coefficient.

a positive correlation with the extent of C4 deposit in the glomerulus (r=0.20, *P*=0.041). Similarly, the level of IgM-aCLs exhibited negative correlations with serum C3 and C4 concentrations (r=−0.19, *P*=0.043; r=−0.21, *P*=0.036, respectively).

In the logistic regression model, no clinical or pathological variables were involved in the regression model with aPL as a dependent variable. However, when IgG-aCL was chosen as a dependent variable, serum C3 was included in the regression model. The findings indicated that serum C3 was independently correlated with IgG-aCL (OR=0.93, *P*=0.015) (Table 5).

Table 5 Binary Logistic Regression Analysis with IgG-aCL as the Dependent Variable

Variable	OR	95% CI for OR	P-value
Serum C3	0.93	0.91–0.99	0.015*
Serum C4	0.85	0.72–0.99	0.214
Hematuria	1.52	0.08–4.36	0.454
WBC	1.04	0.71–10.27	0.172
Hemoglobin	0.98	0.96–1.01	0.426
SLEDAI	0.88	0.76–2.08	0.528
C3 deposition	1.30	0.68–2.48	0.421
C 4deposition	1.17	0.58–10.7	0.384
C1q deposition	1.57	0.30–3.27	0.472
Cellular crescent	1.12	0.85–1.27	0.713

Note: *p<0.05.
Abbreviations: aCL, anticardiolipin; WBC, white blood cell; SLEDAI, SLE Disease Activity Index; OR, odds ratios; CI, confidence interval.

Discussion

In our research, we observed a 44.7% positivity rate of aPLs in LN patients. Notably, many previous studies omitted the measurement of anti-β2-GPI, IgA-aCL, or IgA-anti-β2-GPI antibodies. Consequently, the aPLs positivity rate in our study aligns closely with that reported in earlier studies of LN patients.[11–13]

The SLEDAI has proven to be a reliable tool for monitoring lupus disease activity. In our current study, patients positive for aPLs exhibited a significantly higher SLEDAI compared to their aPLs-negative counterparts. This finding is consistent with some reports that have demonstrated a correlation between aPLs level and disease activity in SLE.[14,15] However, it is worth noting that there are contrasting results in other studies,[16] and this discrepancy may stem from differences in study populations or varying types of aPLs.

Our study also unveiled a higher prevalence of hematuria in the aPLs-positive group, indicating potential proliferative lesions in the glomerulus. While no obvious difference in the kidney activity index was noted between the two groups, the aPLs-positive group exhibited a higher activity index and lower chronicity index than the aPLs-negative group. Additionally, the aPLs-positive group presented with more proliferative lesions (class III and IV). Previous studies, albeit not universally, have suggested a robust correlation between aPLs and renal involvement, particularly glomerular microthrombosis.[5,17] These findings underscore the potential of aPLs as a valuable marker for monitoring LN activity.

Furthermore, our results revealed that aPLs-positive patients exhibited lower serum C3 and C4 concentrations compared to aPLs-negative patients. The levels of different aPLs, particularly IgG-aCL, exhibited a negative association with serum C3 and C4 concentrations, and a positive association with complement deposition in the kidney. In logistic regression analysis, serum C3 emerged as independently associated with IgG-aCL.

The pathogenesis of LN has been attributed, in part, to complement activation through immune complex deposits in the glomerulus, underscoring the significance of immune complex deposits and complement activation in LN.[18] Although anti-ds DNA antibody has been recognized for its potential role in this progression,[19] the involvement of aPLs in this process remains incompletely explored. Some studies suggest that aPLs may contribute to glomerular microthrombosis in LN and may participate in complement activation.[20,21] Additionally, the activation of the complement cascade by aPLs has been implicated in fetal loss and thrombosis in primary/secondary APS patients, challenging the notion that tissue damage in APS is solely driven by thrombosis.[22,23]

In conditions such as SLE or other immune complex-related disorders, the formation of immune complexes can stimulate the classical pathway.[24,25] These immune complexes may encompass an antiphospholipid antibody-antigen complex, with circulating immune complexes amplifying the initiation of complement activation, eventually resulting in thrombotic events, pregnancy morbidity, or even LN. Hence, our findings provide partial support for the idea that complement activation may be triggered by an aPL-autoantigen complex.

Nevertheless, this study has several limitations. The sample size was relatively small, lupus anticoagulants were not measured due to the unavailability of the test in our hospital, aPLs were assessed at a single time point, precluding insights into their role in disease monitoring or prognosis, and the assessment of complement activation factors was restricted, preventing the identification of the predominant complement activation pathway. Future prospective studies with larger cohorts are imperative to address these limitations.

In conclusion, our findings indicate that aPLs may serve as a valuable marker for monitoring LN activity. Specifically, IgG-aCLs may participate in the activation of classical complement pathways.

Data Sharing Statement

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by funds from Public benefit project of Lishui (2021GYX19), Medical and Health Project of Zhejiang (2023583325), Zhejiang Science and Technology (2022C03172), and National-Zhejiang Administration of Traditional Chinese Medicine cooperation project (GZY-ZJ-KJ-23099). This study was also supported by Hubei Province Science and Technology Key R&D Program (2022BCE048), and Qianjiang City, Hubei Province Public Welfare Industry Scientific Research Program(2022GYX002).

Disclosure

The authors declare that there is no conflict of interest for this work.

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