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Original Article

ORIGINAL ARTICLE

Deciphering three predominant biopsy-proven phenotypes of IgG4-associated kidney disease: a retrospective study

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ABSTRACT

Background. IgG4-associated kidney disease (IgG4-RKD) encompasses a spectrum of disorders, predominantly featuring tubulointerstitial nephritis (TIN) and membranous glomerulonephropathy (MGN). The limited understanding of the co-occurrence of IgG4-RD-TIN with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) poses a diagnostic and therapeutic challenge.

Methods. We examined 49 cases, comprising 21 cases of IgG4-RD-TIN (group A), 10 cases of IgG4-RD-TIN accompanied with MGN (group B), and 18 cases of IgG4-RD-TIN concurrent with AAV (group C), at the First Affiliated Hospital of Zhejiang University, China, from June 2015 to December 2022.

Results. The mean age and gender of the three IgG4-RKD subtypes were not statistically significant. IgG4-RD-TIN exhibited higher serum creatinine and a higher incidence of hypocomplementemia (group A 47.6%, group B 30%, group C 16.7%). IgG4-RD-TIN-MGN was characterized by proteinuria (group A 0.3 g/d, group B 4.0 g/d, group C 0.8 g/d, $P < 0.001$) and hypoalbuminemia. IgG4-RD-TIN-AAV exhibited hypohemoglobinemia (group A 103.45 g/l, group B 119.60 g/l, group C 87.94 g/l, $P < 0.001$) and a high level of urine erythrocytes. The primary treatment for IgG4-RD-TIN was steroids alone, whereas IgG4-RD-TIN-MGN and IgG4-RD-TIN-AAV necessitated combination therapy. Group A experienced two relapses, whereas groups B and C had no relapses. There was no significant difference in patient survival among the three groups, and only two cases in group C suffered sudden death.

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Conclusions. This study provides valuable insights into clinical manifestations, auxiliary examination features, pathological characteristics, and prognosis of IgG4-RD-TIN, IgG4-RD-TIN-MGN, and IgG4-RD-TIN concurrent AAV. Large-scale studies are required to validate these findings.

Keywords: anti-neutrophil cytoplasmic antibodies associated vasculitis, IgG4 related disease, IgG4-associated kidney disease, membranous glomerulonephropathy, tubulointerstitial nephritis

KEY LEARNING POINTS

What was known:

- Currently, the understanding of three IgG4-RKD subtypes is incomprehensive.

This study adds:

- The clinical manifestations and results of auxiliary examination varied among the three IgG4-RKD subtypes.

Potential impact:

- All three IgG4-RKD subtypes had effective treatment, with a clinical cure rate of 47/49 (95.6%), and no patient mortality.

INTRODUCTION

IgG4-related disease (IgG4-RD) represents a chronic, progressively inflammatory condition characterized by fibrosis, featuring storiform fibrosis and the infiltration of numerous IgG4-positive plasma cells. IgG4-RD is frequently identified with elevated serum IgG4 concentrations [1, 2] and an IgG4/IgG ratio exceeding 10%, with a specificity of 91% indicative of IgG4-RD [3]. Moreover, IgG4-RD exhibits a predilection for forming tumefactive lesions across multiple organs, including the pancreas, lacrimal glands, salivary glands, kidneys, lungs, retroperitoneum, periaorta, skin, and lymph nodes [4, 5].

The prevalence of kidney involvement in IgG4-RD ranges from 6.9% to 27.4% [6]. Clinical manifestations of IgG4-related pyelitis or retroperitoneal fibrosis encompass inflammatory pseudo-tumor, nephrotic syndrome, renal function impairment, and urinary tract obstruction [7]. Renal involvement comprises two distinct entities collectively termed IgG4-associated kidney disease (IgG4-RKD): tubulointerstitial nephritis (IgG4-RKD-TIN) and glomerular disease, particularly membranous nephropathy (IgG4-RKD-MGN). IgG4-RKD-TIN manifests as mild proteinuria, microscopic hematuria, hypocomplementemia, and renal function decline. By contrast, IgG4-RKD-MGN is characterized by substantial proteinuria without leukocytosis or leukocyte tube type. IgG4-RKD is most sensitive to steroids, and a few diseases can also be treated with immunosuppressive drugs or rituximab. However, Chaba *et al.* reported that the recurrence rate of IgG4-RKD was as high as 34%, and the number of organs involved and the presence of hypocomplementemia were high risk factors for recurrence. Meanwhile, age, peak serum creatinine, and IgG4 level were also highly correlated with the severity of IgG4-RKD [8, 9]. Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a systemic vasculitis marked by small vessel pauci-immune vasculitides and the presence of circulating pathogenic ANCA, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [10]. ANCA is a group of autoantibodies that target myeloperoxidase (MPO) and proteinase 3 (PR3) [11]. AAV, particularly GPA [12] and EGPA [13], may mimic IgG4-RD because of elevated serum IgG4 and similar pathological features. Additionally, there is evidence suggesting a potential overlapping syndrome with patients meeting the criteria for both IgG4-RD and AAV [14]. In this scenario, the pathological tissue of IgG4-RD contains >10 IgG4-positive plasma cells secreting a large amount of IgG4, and the MPO of this AAV type is the IgG4 subtype. In the present study, the pathology of a patient group showed the characteristics of IgG4-RD (IgG4-positive plasma cells >10/HPF and storiform fibrosis) and AAV (crescent formation, glomerular capillary necrosis, and fibrinous exudation necrosis of renal vessels) therefore, we regarded this type of IgG4-RD accompanied by AAV as a special type of IgG4-related nephropathy [15].

To our knowledge, there is a dearth of literature describing and comparing the clinical manifestations, auxiliary examination features, and pathological characteristics of IgG4-RD-TIN, IgG4-RD-TIN-MGN, and IgG4-RD-TIN concurrent AAV. This study provides a comprehensive analysis of biopsy-proven IgG4-RD cases from June 2015 to December 2022.

MATERIALS AND METHODS

Study population and data

Between June 2015 and December 2022, 93 renal biopsies were conducted at the First Affiliated Hospital of Zhejiang University, China, because of elevated blood IgG4 levels. Among these, 38 renal biopsies lacked IgG4 plasma cells, and the remaining 55 renal biopsies met the criteria. Excluded cases comprised various conditions: one case of pancreatic cancer, one case of hygrocyte tumor, two cases of Castleman's disease, one case with gastric cancer and one case of confirmed systemic lupus erythematosus. The final study cohort included 49 cases: 21 cases of IgG4-RD-TIN (group A), 10 cases of IgG4-RD-TIN-MGN (group B), and 18 cases of IgG4-RD-TIN concurrent AAV (group C) (18 cases of MPA) (Fig. 1), with six cases from group C previously featured in the 2019 article by Ma *et al.* [15].

We conducted a comprehensive evaluation of patients, considering general conditions (age and sex), clinical manifestations, and extrarenal involvement based on auxiliary examinations. Laboratory test indicators encompassed white blood cells, hemoglobin, percentage of neutrophils, platelets, percentage of eosinophils, liver and kidney function, electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR),

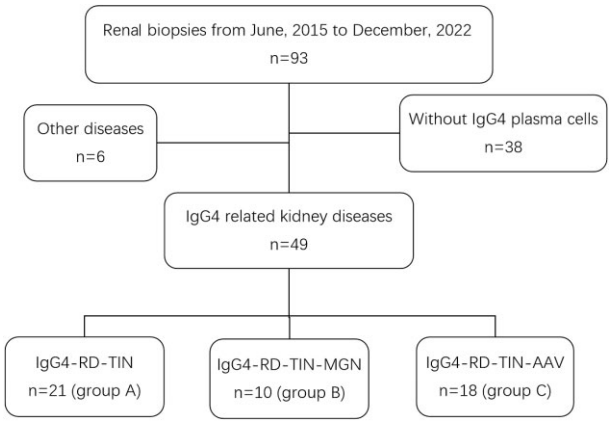

Figure 1: Study flow chart.

urine routine and specific gravity, total IgE, IgG, IgG4, complement 3, complement 4, MPO, PR3, p-ANCA, c-ANCA, antinuclear antibodies (ANA), urinary IgG, urinary retinol-binding protein, urine microalbumin, urinary beta-2 microglobulin, and 24-hour urine protein. Pathological features included assessments through light microscopy, electron microscopy, and immunofluorescence. Treatment, prognosis, and follow-up data were systematically collected; relapse was defined as the progression or recurrence of clinical symptoms, biological abnormalities, or imaging findings after remission.

Diagnostic criteria

IgG4-related diseases were defined in accordance with the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria (ACR/EULAR) [16], IgG4-RKD was confirmed using 2011 IgG4-RKD diagnostic criteria [17], and Raissian diagnostic criteria [18]. The definition of AAV comes from the 2012 Chapel Hill Consensus Conference on nomenclature of vasculitides [19–21]. The estimated glomerular filtration rate was calculated using the Kidney Disease Diet Modification (MDRD) formula, defined as MDRD-GFR = $186 \times [(\text{Scr}/88.4)^{(-1.154)}] \times [\text{age}^{(-0.203)}\ (\text{female} \times 0.742)]$.

Statistical analysis

SPSS v.26.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Continuous variables are expressed as mean ± standard deviation or medians and minimum and maximum range. The difference in numerical data conformed to a normal distribution, and Student's *t*-test was used. Semi-quantitative scores were compared using the Mann–Whitney *U*-test. Categorical data, which are expressed in counts and percentages, were compared using Chi-square tests or Fisher exact tests as appropriate. Two-tailed *P* values of <0.05 were considered significant.

RESULTS

Demographics and clinical characteristics

Table 1 outlines the general conditions and clinical manifestations, including extrarenal involvement, of groups A, B, and C. No significant differences were observed in gender and age distribution. Group B exhibited shorter hospitalization days (median 4 days) compared with group A (median 11 days) and group C (median 10 days) ($P = 0.043$). These three IgG4-RKD groups had different chief complaints during admission. Elevated serum creatinine was the most common manifestation in group A, one-third in group C, and none in group B. The common clinical manifestations in group B were proteinuria and hematuria. All three groups had extrarenal organ involvement, but there was no statistical difference in the type and number of extrarenal-involved organs (group A 85.7%; group B 50%; group C 61.1%; $P = 0.083$). Commonly affected extrarenal organs included the hepatobiliary and pancreatic system (30.6%), lymph nodes (53.1%), and lungs (24.5%).

Laboratory index characteristics

Table 2 presents the serological indicators, demonstrating no significant differences in parameters among the three groups, including white cell count, percentage of neutrophils, percentage of eosinophils, serum creatinine, uric acid, and ESR. Hemoglobin levels varied significantly among the three groups ($P < 0.001$), with group C exhibiting significantly lower levels (mean 88 g/L). Platelet counts in group C were significantly higher than those in groups A and B ($P = 0.011$). The serum total protein and albumin levels in group B were notably lower than those in groups A and C ($P = 0.014$ and 0.008, respectively). CRP levels in group C were significantly higher than those in groups A and B ($P < 0.001$).

No statistical differences were observed regarding urine indexes in groups A, B, and C, including pH, urine specific gravity, urinary IgG, urinary retinol-binding protein, and urine microalbumin. Urine red blood cell counts increased in all three groups, with a more significant increase noted in group C ($P = 0.004$). Differences in urinary $\beta 2$ globulin and 24-hour urinary protein were evident among the three groups. $\beta 2$ globulin levels in group B were significantly lower than those in the other two groups ($P = 0.013$), whereas the 24-hour urinary protein in group B was significantly higher than those in the other two groups ($P < 0.001$).

Hypocomplementemia was present in 47.6% (10/21) of patients in group A (four patients with low C3 and six patients with low C3 and C4) and 30% (3/10) of patients in group B (two patients with low C4 and one patient with low C3 and C4), whereas hypocomplementemia was present in 16.7% (3/18) of patients in group C (two patients with low C3 and one patient had low C3 and C4). However, immunological indexes, including total IgE, IgG, complement 3, complement 4, PR3, and p-ANCA, showed no significant difference among the three groups. Serum IgG4 levels were increased in all three groups, with group A exhibiting the highest levels than groups B and C ($P = 0.009$). MPO levels within the normal range were observed in groups A and B, whereas MPO in group C was significantly increased ($P < 0.001$). C-ANCA was negative in both groups A and B, with 22.2% of cases in group C testing positive ($P = 0.024$). A significant difference in ANA was noted, with 52.4% (11/21) in group A, 10% (1/10) in group B, and 16.7% (3/18) in group C ($P = 0.016$).

Pathological features

The common pathological features of the three groups were all with IgG4-positive plasma cells >10/HPF and no obliterating phlebitis. In group A, 6/21 cases had storiform fibrosis, whereas groups B and C exhibited no storiform fibrosis (Fig. 2). The mean glomerular sclerosis ratios were 29.5% in group A, 17.4% in group

Table 1: Comparison of general conditions and clinical manifestation of groups A, B, and C.

Variable	Overall ($n = 49$)	Group A ($n = 21$)	Group B ($n = 10$)	Group C ($n = 18$)	P
Male, *n* (%)	37 (75.5)	18 (85.7)	8 (80.0)	11 (61.1)	0.191
Age, years (SD)	65 ± 9	66 ± 9	63 ± 10	66 ± 8	0.589
Length of stay, days (IQR)	9 (5, 14)	11 (7, 14)	4 (2, 8)	10 (7, 17)	0.043
Chief complaint, *n* (%)					0.000
Creatinine elevation	22 (44.9)	16 (76.2)	0	6 (33.3)	
Proteinuria	9 (18.4)	4 (19)	5 (50)	0	
Hematuria	2 (4.1)	0	2 (20)	0	
High blood pressure	1 (2)	1 (4.8)	0	0	
Fatigue	7 (14.3)	1 (4.8)	1 (10)	5 (27.8)	
Nocturnal enuresis	2 (4.1)	1 (4.8)	1 (10)	0	
Edema	15 (30.6)	3 (14.3)	3 (30)	9 (50)	
Fever	3 (6.1)	0	0	3 (16.7)	
Others	15 (30.6)	7 (33.3)	1 (10)	7 (38.9)	
Extrarenal involvement, *n* (%)	34 (69.4)	18 (85.7)	5 (50)	11 (61.1)	0.083
Extrarenal-involved organs, *n* (%)					0.217
Pancreato-hepato-biliary	15 (30.6)	10 (47.6)	1 (10)	4 (22.2)	
Lymph nodes	26 (53.1)	13 (61.9)	4 (40)	9 (50)	
Lung	12 (24.5)	4 (19)	1 (10)	7 (38.9)	
Orbital	1 (2)	1 (4.8)	0	0	
Sinusitis	3 (6.1)	1 (4.8)	2 (20)	0	
Retroperitoneum and aorta	3 (6.1)	1 (4.8)	1 (10)	1 (5.6)	

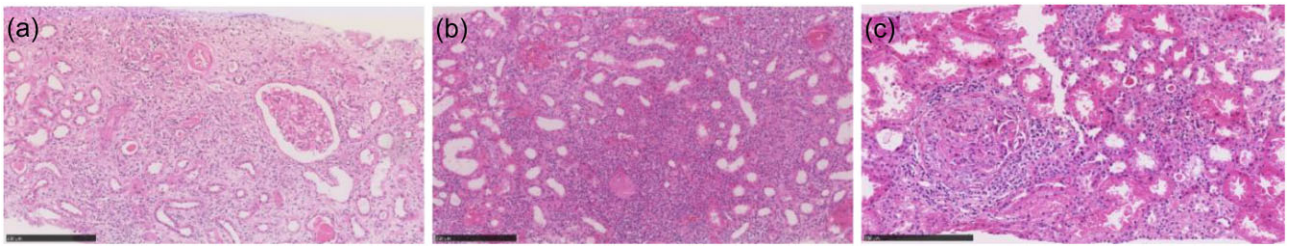

Figure 2: Pathological features of group A, group B, and group C. H&E staining of IgG4-RD-TIN showed 2/15 (13.3%) glomerular sclerosis, storiform fibrosis, IgG4-positive plasma cells >10/HPF, and CD138$^+$ (**a**). H&E staining of IgG4-RD-TIN-MGN showed 7/23 (30.4%) glomerular sclerosis, IgG1, IgG4, and C3 deposits, IgG4-positive plasma cells >10/HPF, and CD138$^+$ (**b**). H&E staining of IgG4-RD-TIN-AAV showed 7/27 (25.9%) glomerular sclerosis, six cellular crescent (22.2%), one mixed crescent (3.7%), two segmental crescent (7.4%), eight glomerular necrosis, and IgG4-positive plasma cells >10/HPF (**c**).

B, and 25.3% in group C. In group B, three patients had pathologically positive phospholipase antibodies but negative serum PLA2R antibodies. The unique pathological features of IgG4-RD-TIN-AAV were crescent formation in different degrees, glomerular capillary necrosis, and fibrinous exudation necrosis of renal vessels (Supplementary Table).

Treatment and prognosis

The treatment regimens significantly differed among the three groups ($P < 0.001$) (Fig. 3). Predominantly used treatments across the three groups included steroids, steroids combined with rituximab, and steroids combined with cyclophosphamide. The median serum creatinine levels at admission in groups A, B, and C were 251, 100, and 165 μmol/l, respectively, but there was no statistical significance. The mean serum creatinine at the last follow-up in groups A, B, and C were 185.8, 88.8, and 131.7 μmol/l, respectively, which is lower than serum creatinine at admission. There were no statistically significant differences in serum creatinine at admission and 1 month, whereas significant variations emerged at 3, 6, and 12 months ($P < 0.05$), with serum creatinine in group A notably higher than that in B and C groups (Fig. 4a). During the whole follow-up, the GFR of group B was the highest, and that of group A was the lowest. There were statistical differences in GFR among the three groups ($P < 0.05$) (Fig. 4b). Hemoglobin at the end of follow-up in all three groups (group A 109.4 g/l, group B 131.6 g/l, group C 114.6 g/l), which is higher than hemoglobin at admission (group A 103.5 g/l, group B 119.6 g/l, group C 87.9 g/l). At the end of follow-up, IgG4 was lower, and albumin was higher in the three groups than at admission (Fig. 4c and d). The median of 24-hour urine protein quantitation in group B at admission was 4 g, and the mean protein/creatinine ratio at the end of follow-up was 0.4. The MPO in group C decreased significantly after treatment (75.2 RU/ml at admission, 17.2 RU/ml at the end of follow-up). Recurrence rates and patient survival exhibited no significant differences among the three groups, with only two relapses occurring in the group A. Among the 49 cases in this study, two deaths were recorded, both attributed to sudden cardiac death.

Table 2: Comparison of laboratory indexes of groups A, B, and C.

Variable	Overall ($n = 49$)	Group A ($n = 21$)	Group B ($n = 10$)	Group C ($n = 18$)	*P*
White cell count, 10^9/l (SD)	7.19 ± 2.65	6.76 ± 2.63	6.04 ± 1.46	8.31 ± 2.87	.058
Hemoglobin, g/l (SD)	101 ± 22.03	103.45 ± 21.02	119.60 ± 16.69	87.94 ± 17.58	.000
Neutrophile granulocyte, % (SD)	65.6 ± 16.3	66.2 ± 12.5	60.4 ± 15.1	67.9 ± 20.4	.504
Platelet count, 10^9/l (SD)	211.7 ± 87.82	179.70 ± 58.11	190.20 ± 100.93	259.28 ± 91.01	.011
Eosinophilic granulocyte, % (IQR)	2 (1, 4)	1.85 (1.23, 3.25)	2.35 (1.00, 7.78)	1.75 (0.28, 3.60)	.864
Serum Cr, umol/l (IQR)	151 (110, 296)	251 (130, 387)	100 (73, 124)	165 (109, 265)	.059
Uric acid, umol/l (SD)	373.76 ± 112.44	396.29 ± 100.35	366.80 ± 118.08	351.33 ± 123.62	.459
Total protein, g/l (SD)	67.29 ± 12.55	73.01 ± 13.85	60.89 ± 11.51	64.18 ± 8.58	.014
Serum albumin, g/l (SD)	30.88 ± 6.44	34.04 ± 5.71	27.73 ± 7.23	28.93 ± 5.38	.008
CRP, mg/l (IQR)	10 (3.65, 52.40)	4.80 (3.10, 14.60)	4.55 (2.73, 10.38)	59.50 (14.98, 90.31)	.000
ESR, mm/h (SD)	71.64 ± 39.34	70.80 ± 37.84	57.78 ± 42.69	79.50 ± 39.52	.406
PH (SD)	5.76 ± 0.93	5.83 ± 0.54	5.55 ± 1.74	5.79 ± 0.61	.737
Urine specific gravity (SD)	1.01 ± 0.01	1.01 ± 0.01	1.02 ± 0.01	1.01 ± 0.00	.086
Urine erythrocyte,/μl (IQR)	20.8 (3.3, 112.3)	3.4 (1.1, 34.6)	15.5 (5.9, 95.9)	34.6 (21.1, 277.8)	.004
Total IgE, KU/L (IQR)	199 (56, 861)	191 (59, 875)	861 (284, 2468)	64 (28, 395)	.170
IgG, mg/dl (SD)	2144.39 ± 1082.09	2450.67 ± 1380.92	1917.50 ± 793.61	1913.11 ± 725.59	.233
IgG4, g/l (IQR)	4.8 (3.3, 10.3)	7.4 (4.8, 13.7)	4.5 (2.8, 12.5)	3.5 (2.6, 4.9)	.009
Serum complement 3, mg/dl (SD)	82.70 ± 31.88	70.41 ± 31.40	87.67 ± 26.50	94.28 ± 31.53	.054
Serum complement 4, mg/dl (SD)	20.16 ± 17.13	14.47 ± 9.17	18.80 ± 11.83	27.56 ± 23.59	.053
MPO, RU/ml (IQR)	3.9 (2.2, 67.2)	2.7 (1.4, 3.9)	2.4 (2.1, 3.1)	75.2 (38.8, 90.3)	.000
PR3, RU/ml (SD)	3.49 ± 2.95	3.72 ± 3.7	3.30 ± 2.01	3.32 ± 2.44	.904
p-ANCA, *n* (%)	9 (18.4)	3 (14.3)	0	6 (33.3)	.075
c-ANCA, *n* (%)	4 (8.2)	0	0	4 (22.2)	.024
ANA, *n* (%)	15 (30.6)	11 (52.4)	1 (10)	3 (16.7)	.016
Urinary IgG, g/mol.Cr (IQR)	7.6 (4.2, 15.4)	5.6 (2.6, 13.0)	8.6 (3.2, 342.7)	9.6 (5.0, 19.6)	.363
Urinary retinol-binding protein, g/mol.Cr (IQR)	0.5 (0.1, 3.0)	0.4 (0.1, 6.9)	0.1 (0.0, 2.3)	0.6 (0.3, 2.0)	.578
Urine microalbumin, g/mol.Cr (IQR)	20.6 (9.0, 74.1)	13.3 (6.9, 37.2)	55.5 (13.8, 591.1)	42.4 (13.9, 120.0)	.099
Urinary beta-2 microglobulin, g/mol.Cr (IQR)	0.5 (0.1, 4.9)	0.7 (0.1, 9.8)	0.0 (0.0, 0.2)	1.7 (0.2, 5.5)	.013
24-hour urine protein, g (IQR)	0.8 (0.3, 1.7)	0.3 (0.2, 0.9)	4.0 (2.1, 10.6)	0.8 (0.5, 1.3)	.000

ANCA, anti-neutrophil cytoplasmic antibodies; Cr, creatinine; Ig, immunoglobulin

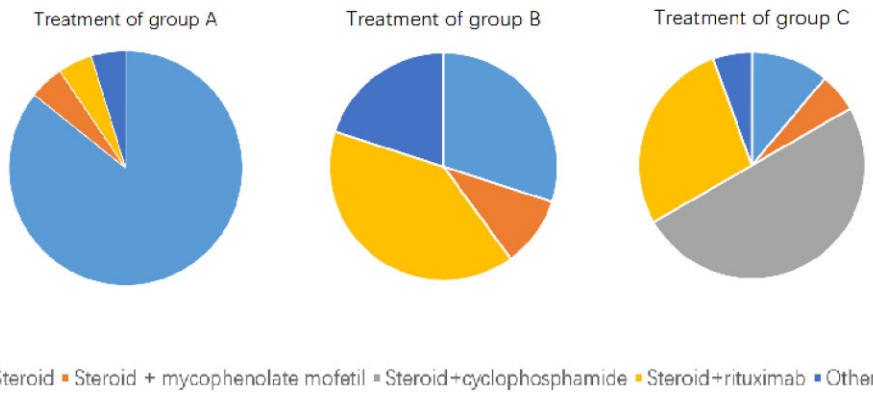

Figure 3: The treatments of group A, group B, and group C. In group A, steroid alone accounted for 85.7%, steroid combined with mycophenolate mofetil, steroid combined with rituximab, and leflunomide accounted for 4.8% each. In group B, steroid combined with rituximab accounted for 40%, steroid alone accounted for 30%, steroid combined with mycophenolate mofetil and other treatments accounted for 10% and 20%, respectively. In group C, steroid combined with cyclophosphamide accounted for 50%, steroid combined with rituximab accounted for 27.8%, steroid alone accounted for 11.1%, steroid combined with mycophenolate mofetil and other treatments accounted for 5.6% each.

DISCUSSION

This study's strength lies in its comprehensive inclusion of cases with pathological biopsy results, presenting many IgG4-RKD cases, and exclusively focusing on IgG4-RD-TIN, affirming TIN as the predominant and widespread pathological subtype of IgG4-RKD. Distinct clinical manifestations characterized the three types of nephropathy associated with IgG4-RD. All three groups exhibited increased serum IgG4, where the IgG4 degree was notably higher in IgG4-RD-TIN. IgG4-RD-TIN primarily manifested with elevated serum creatinine and lower C3 and C4 levels. IgG4-RD-TIN-MGN prominently featured massive proteinuria and hypoalbuminemia. By contrast, IgG4-RD-TIN-AAV displayed different clinical manifestations, including low hemoglobin, high platelets, significantly increased hypersensitive CRP, and positive urine erythrocytes. The group A exhibited persistent high

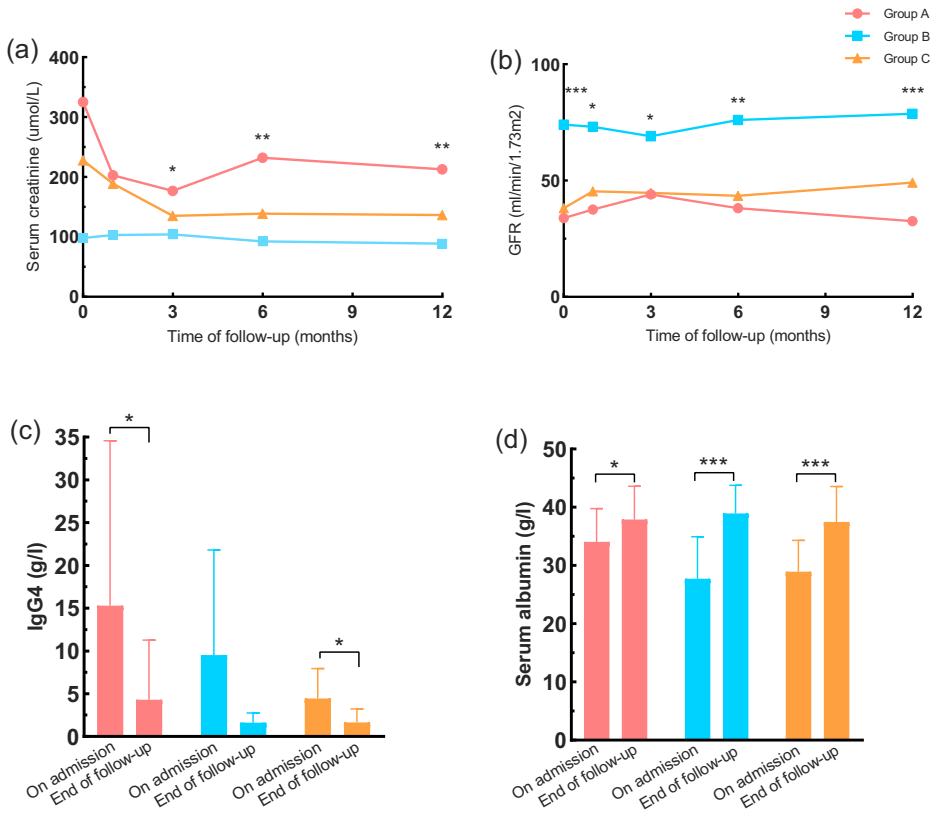

Figure 4: There was no statistical difference in serum creatinine among groups A, B, and C on admission and 1 month. However, statistical significance emerged in serum creatinine levels at 3, 6, and 12 months, with *P* values of 0.011, 0.006, and 0.003, respectively. Notably, the serum creatinine levels in group A were significantly higher than those in the other two groups. (**a**) The GFR of the three groups were statistically different throughout the disease course, with all *P* values <0.05. (**b**) At the end of follow-up, IgG4 was lower and albumin was higher in the three groups than at admission (**c**, **d**).

creatinine levels at follow-up, whereas the vasculitis group initially presented high creatinine levels that subsequently decreased and remained stable.

IgG4-RD is systemic and can affect different organs. Extrarenal organs were involved to a large extent (mean 69.4%) in all three types of IgG4-RKD. The main extrarenal organs involved were the hepatobiliary and pancreatic system (30.6%), lymph nodes (53.1%), and lungs (24.5%). IgG4, which is associated with three nephropathy and tubulointerstitial nephritis, was 100% present, as Saeki *et al.* reported that IgG4-RD-TIN was the most dominant feature of IgG4-RKD [22]. Previous reports have shown that 7%–10% of IgG4-RD-TIN combined with MGN, but in the present study, the incidence of IgG4-RD-TIN-MGN was 10/49 (20.4%), indicating a significantly increased incidence and the combined IgG4-RD-TIN-AAV was 18/49 (36.7%).

Serum creatinine levels in pure IgG4-RD-TIN were significantly higher than those in the other two groups. Six months post-discharge, serum creatinine levels in group A remained elevated or increased, in contrast to the decreasing and stable creatinine levels observed in the other two groups. IgG4-RD-TIN-MGN exhibited the lowest creatinine levels mainly because of the following reasons. First, the incidence of low complement in simple IgG4-RD-TIN was 47.5%, which is substantially higher than that in the other two groups. Among the 49 cases, only two recurrence cases also occurred in IgG4-RD-TIN. Previous studies have shown that a low complement degree was related to disease severity and disease activity (remission, recurrence) [23]. Second, pathologically, pure IgG4-RD-TIN patients had more interstitial storiform fibrosis, and the interstitial fibers were irreversible changes. Third, the aforementioned situation may occur because the clinical manifestations of IgG4-RD-TIN were less than those in the other two groups. Significant clinical manifestations of IgG4-RD-TIN-MGN and IgG4-RD-TIN-AAV (e.g. manifestations of proteinuria, hematuria, hypoproteinemia, and edema) led to increased vigilance, admission to hospital in the early stages of the disease, less renal impairment, better response to treatment, and lower recurrence rates. Fourth, the use of steroids alone in this patient group of remains to be further observed whether stronger immunosuppression (such as rituximab) can achieve better results in this patient group clinically.

PLA2R is crucial for distinguishing primary MGN from secondary MGN. PLA2R-positive MGN was regarded to be primary MGN; conversely, PLA2R-negative MGN was secondary MGN. Studies have shown that only 75%–80% of primary MGN PLA2R is positive [24]. Thus, PLA2R negative MGN may also be the primary MGN. In the present study, three cases of IgG4-RD-TIN-MGN were PLA2R positive. However, the recent ACR/EULAR IgG4-RD classification criteria consider anti-PLA2R as an exclusion criterion for the diagnosis of IgG4-RD [16]. PLA2R-positive IgG4-RD-MGN has also been reported in previous studies [25]. We diagnosed the three cases as secondary MGN based on the following evidence: first, all three cases were IgG4-RD-TIN; second, all extrarenal organs were involved; and third, the cases were all supported by pathological findings. The cause and mechanism of PLA2R positive in IgG4-RD-TIN-MGN must be further studied.

ANCA positivity is one of the exclusion criteria proposed for IgG4-RD diagnosis in ACR/EULAR IgG4-RD classification criteria [16]. ANCA is critical for the differential diagnosis between AAV and IgG4-RD, but low-titer ANCA is present in several autoimmune disorders, including IgG4-RD. Accordingly, IgG4 ANCA detection has been considered as a possible tool for diagnosis. However, in the 18 cases of IgG4-RD-TIN-AAV in the present study, the comprehensive clinical manifestations, serology, imaging, and pathology met the diagnosis of both IgG4-RD and AAV. Recent studies have demonstrated an overlap in the clinical characteristics of IgG4-related disease and AAV. A common pathophysiological pathway of IgG4-RD and AAV may involve T follicular helper cells, which are shown to increase and polarize toward follicular helper T cells-2 subtype in both diseases, enhancing IgG4-plasma cell polarization [26]. On the one hand, six of the 18 IgG4-RD-TIN-AAV patients were p-ANCA positive, and four were c-ANCA positive. ANCA positivity and other autoantibody changes in IgG4-RD are thought to be a side phenomenon because of chronic non-pathogenic autoantibody accumulation inflammation [27]. Previous reports have disclosed that ANCA is mainly IgG1 and IgG4 isotypes, and the incidence of IgG4 elevation is linked to the specific type of AAV (89% for GPA, 20%–75% for MPA, and 75%–80% for EGPA) [13, 28, 29]. Our previous study demonstrated that the IgG4 subclass of MPO-ANCA was higher in the concomitant group than in the AAV alone group. A merge of IgG4 and MPO immunofluorescence was observed in parts of the mesangium of concomitant AAV and IgG4-RD patients. IgG4 subclass of ANCA may be a pathogenic factor [13]. On the other hand, Bravais *et al*. suggested that the IgG4 production found in IgG4-RD might promote the development of AAV in some specific way [30]. The significance of elevated IgG4 is associated with disease activity and chronic inflammation in both IgG4-RD and AAV. However, IgG4 plays a role in inhibiting inflammation rather than activating inflammation in IgG4-RD. B-cells producing ANCA autoantibodies are selected in an inflamed microenvironment and mature into pathogenic plasma cells producing proinflammatory ANCA. This role in local inflammation might be the early acute lesion in AAV-associated glomerulonephritis [31]. Therefore, the relationship between IgG4-RD and AAV must be further clarified.

In summary, this study contributes valuable insights into the clinical manifestations, auxiliary examination features, and pathological characteristics of IgG4-RD-TIN, IgG4-RD-TIN-MGN, and IgG4-RD-TIN concurrent AAV. Large-scale studies are warranted to validate these findings and enhance our understanding of these diseases.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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DATA AVAILABILITY STATEMENT

Research data may be obtained through the corresponding author for reasonable reasons.

CONFLICT OF INTEREST STATEMENT

No conflict of interest exits in the submission of this manuscript.

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