Glomerular Diseases

Research Article

Glomerular Dis 2023;3:32–41
DOI: 10.1159/000528712

Received: August 17, 2022
Accepted: December 6, 2022
Published online: December 21, 2022

Autoimmunity in Infection-Related Glomerulonephritis

Hae Yoon Grace Choung[a] Rickinder Grewal[b]

[a]Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [b]Department of Medicine, Division of Nephrology, University of Rochester Medical Center, Rochester, NY, USA

Keywords
Infection-related glomerulonephritis · Lupus-like nephritis · Autoimmunity · Postinfectious glomerulonephritis · Glomerular disease

Abstract
Introduction: Autoimmune (AI) reactivity in the setting of infection-related GN (IRGN) is often viewed as an epiphenomenon and is not well described. ***Methods:*** We report a cohort of 17 patients with IRGN during a 7-year period that highlights cases with AI reactivity and describes the clinical and pathologic characteristics of IRGN cases associated with AI reactivity. ***Results:*** Of the IRGN cases, 76% had clinical evidence of an autoimmune disease (AD) and/or positive AI serologies. Within the IRGN group with AI reactivity, 12 had positive AI serologies (92%) and 10 had AD (77%). 30% had a prior diagnosis of AD, while the remaining 70% did not have a history of AD and were either diagnosed or suspected of having an AD at the time of biopsy. The most common autoantibody detected was anti-nuclear antibody followed by anti-neutrophil cytoplasmic antibodies and autoantibodies associated with antiphospholipid syndrome. ***Conclusion:*** The study is not sufficiently powered to determine any significance but demonstrates the frequency with which AI features occur in IRGN and should prompt further future investigation. In summary, our findings suggest AI manifestations are common in IRGN.

Introduction

Multiple studies have linked infections with autoimmunity through various possible mechanisms [1]. Yet autoimmune (AI) reactivity in the setting of infection-related GN (IRGN) is often viewed as an epiphenomenon that occasionally aggravates the infectious process [2, 3]. Pathologic features typical of an IRGN are subepithelial hump-shaped deposits by electron microscopy (EM), an exudative proliferative glomerulonephritis by light microscopy (LM), and C3 dominance or co-dominance by immunofluorescence (IF). A subset of these patients with biopsy findings of IRGN demonstrate positive AI serologies and/or a clinical presentation concerning for concomitant autoimmune disease (AD).

This phenomenon is well characterized in endocarditis-associated IRGN, in which anti-neutrophil cytoplasmic antibody (ANCA) seropositivity has been identified in up to 28% of patients and in other various infections including viral (hepatitis B and C), bacterial, fungal, and parasitic [4]. However, the frequency of other positive AI serologies such as anti-nuclear antibody (ANA) or the subsequent development of AD is not well described in cases with IRGN. Moreover, the clinicopathologic presentation and prognosis of those with IRGN and evidence of autoimmunity versus those who do not have AD or AI serologies are not well understood. We sought to further understand the clinicopathologic presentation of patients with IRGN who have positive AI serologies

Karger@karger.com
www.karger.com/gdz

Correspondence to:
Hae Yoon Grace Choung, haeyoon.choung@cshs.org

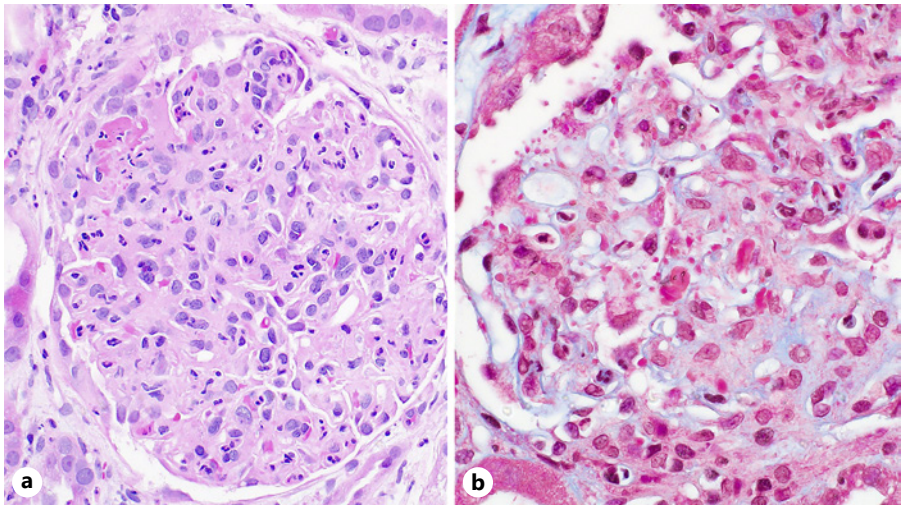

Fig. 1. **a** LM from biopsy of patient #17. Exudative glomerulonephritis with segmental cellular crescents associated with fibrinoid necrosis (H&E, original magnification, × 400). **b** Prominent fuchsinophilic subepithelial deposits (trichrome, original magnification, × 400).

and/or developed AD in the setting of infection by reviewing renal biopsies of patients with the diagnosis of IRGN over a 7-year period.

Materials and Methods

All native kidney biopsies of patients from Strong Memorial Hospital accessioned from 2015 to 2022 were retrospectively reviewed for the presence of IRGN. Demographic and clinical information at the time of biopsy and at last follow-up were collected from electronic medical records and referral forms from the submitting physicians, if available. Clinical data included laboratory parameters such as serum creatinine, presence of proteinuria, urinalysis, abnormal serologies, and recent medical history of infection, other ADs, and neoplasm. The following clinical definitions were used: nephrotic-range proteinuria as a urine protein/creatinine ratio or 24-h urine protein >3.5 g per day; complete recovery as return of serum creatinine to baseline (if available) or to a level ≤1.2 mg/dL; or resolution of proteinuria (or at least to less than 1 g), particularly if the creatinine was normal to begin with; persistent renal dysfunction as persistent elevation of serum creatinine 0.2 mg/dL above baseline or a follow-up serum creatinine of >1.2 mg/dL; end-stage renal disease (ESRD) as requiring renal replacement therapy. Tubular atrophy and interstitial fibrosis were graded as follows: none, 0; mild, 1–25%; mild to moderate, 26–35%; moderate, 36–50%; moderate to severe, 51–60%; severe >60%. Mesangial hypercellularity was defined as > 3 mesangial cells per mesangial area; endocapillary hypercellularity as glomerular capillary luminal narrowing or occlusion by increased cells; extracapillary hypercellularity/crescent as >2 cell layers involving more than 10% of the glomerulus; membranoproliferative pattern as proliferative glomerulonephritis with glomerular basement membrane duplication; and interposition of cells and matrix [5]. The term bacterial IRGN used in this manuscript encompasses acute postinfectious (poststreptococcal) GN, IgA-dominant IRGN, endocarditis-related GN, and shunt nephritis [6]. Other infectious agents including

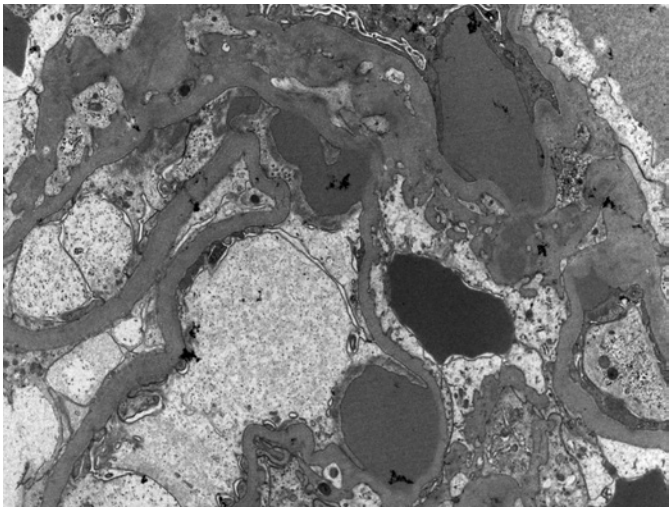

Fig. 2. EM from patient #17 showing subepithelial hump-shaped deposits.

some viruses can also present with morphologic features of IRGN and were therefore included in this study. Features of IRGN included an exudative proliferative glomerulonephritis characterized by prominent neutrophilic infiltration by LM (Fig. 1a–b), subepithelial hump-shaped deposits by EM (Fig. 2), and C3 dominance or co-dominance by IF (Fig. 3a–b).

Cases were reviewed and divided into 2 groups: IRGN with positive AI serologies and/or AD and IRGN without evidence of AI serologies or AD. The pathologic features were then correlated with the clinical findings at the time of biopsy and at latest follow-up (including treatment and outcome).

All renal biopsies were processed using standard techniques for LM, IF, and EM and interpreted by one of three renal pathologists. Consensus was obtained for each case at a weekly conference attended by all three of the renal pathologists. IF staining intensity was graded semi-quantitatively on a scale from 0 to 3+.

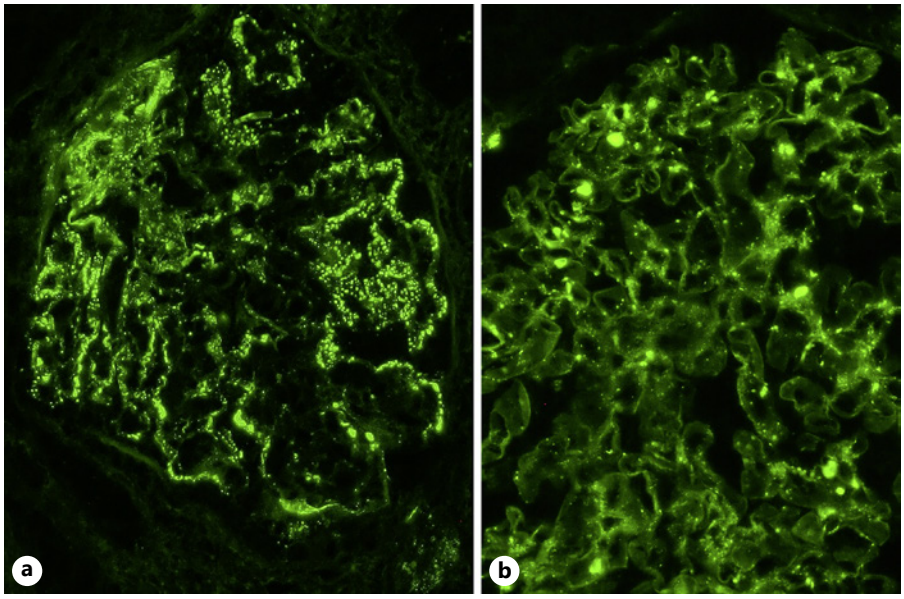

Fig. 3. IF of C3 staining from biopsies of patient #15 with garland pattern (**a**) and patient #16 with "starry sky" (**b**) pattern.

Statistical analysis was performed using SPSS software (version 28). Continuous variables were expressed as mean (± standard deviation), while categorical variables were shown as frequency (%). To compare continuous values between the groups, we performed two-sample *t* tests without assuming equal variances. To compare categorical differences, we created cross-tabulations of each variable against the group and used Fisher's exact test. This study was approved by the Institutional Review Board at the University of Rochester Medical Center (STUDY00007310).

Results

From January 2015 to May 2022, 17 cases with IRGN from Strong Memorial Hospital were identified.

Demographics and Clinical Data

Demographics and clinical data are presented in Tables 1 and 2. More detailed clinical data for AI and non-AI are provided in Table 3. Of the 17 patients with IRGN, 13 had either AD and/or positive AI serologies (AI group), while 4 were negative for AI serologies and without clinical evidence of AD (non-AI group). All patients with IRGN had an average age of 55 ± 21 years and were predominantly male (male:female ratio 7.5:1). Fifty-three percent were Caucasian, 29% were black, 6% were Asian, and 12% were unknown. There were no significant differences in demographics between the 2 groups. In addition, both groups similarly demonstrated evidence of renal insufficiency, nephrotic-range proteinuria, and hematuria at time of biopsy (Table 2). Though there were no statistically significant differences regarding complement levels, 3 cases in the AI cohort exhibited low C3 and C4 in comparison to none of the non-AI patients.

The most common causative agent for IRGN (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528712) was *Streptococcus* (29%), followed by *Staphylococcus* (24%), hepatitis C (HCV; 24%), *Enterococcus* (18%), and human immunodeficiency virus (6%). The AI cohort tended to demonstrate more bacterial infections (69% vs. 25%, $p = 0.3$), while viral infection by HCV was more prominent in the non-AI group (50% vs. 15%, $p = 0.3$). That said, the sample size was too small to draw any significant associations.

Of the IRGN cases, 76% had clinical evidence of an AD and/or positive AI serologies. Within the AI group, 10 cases had AD (77%) and 12 had positive AI serologies (92%). Among those cases with AD, 3 had a history of AD, while 7 were diagnosed or suspected of having an AD while admitted at the time of biopsy. The 3 with a previous history of AD included 1 with relapsing polymyalgia rheumatica, 1 with autoimmune hemolytic anemia, and 1 with active Crohn's disease. The remaining 7 presented with AD at hospitalization without a prior history of autoimmunity including 1 with suspected antiphospholipid syndrome (APS), 5 with ANCA vasculitis, 1 with suspected polymyalgia rheumatica versus giant cell arteritis, 1 with suspected AI myopathy, and 1 with mixed connective tissue disease. Twelve cases had positive AI serologies, of which 62% had ANAs, 46% had ANCAs (not including the 15% with indeterminate), and 29% had miscellaneous

Table 1. Demographics and comorbidities of patients with IRGN

Clinical features	Patients, *n* (%) or mean ± SD		
	IRGN with AI	IRGN without AI	*p* value
Age, years	54±22	58±20	0.8
Gender			1.0
Male	11 (85)	4 (100)	
Female	2 (15)	0 (0)	
Race			0.1
Caucasian	8 (62)	1 (25)	
Black	3 (23)	2 (50)	
Hispanic	0 (0)	0 (0)	
Asian	0 (0)	1 (25)	
Unknown	2 (15)	0 (0)	
Comorbidities			
Diabetes mellitus	6 (46)	1 (25)	0.6
Hypertension	10 (77)	3 (75)	1.0
Coronary artery disease	3 (23)	1 (25)	1.0
Neoplasm	5 (38)	1 (25)	1.0
Cirrhosis	2 (15)	0 (0)	1.0
Drug/alcohol abuse	1 (8)	2 (50)	0.1

Table 2. Clinical presentation of patients with IRGN at time of renal biopsy

	Patients, *n* (%) or mean ± SD		
	IRGN with AI	IRGN without AI	*p* value
Serum creatinine, mg/dL	4.1±2.3	4.5±2.9	0.8
Proteinuria, g/day	6.0±6.1	8.3±6.5	0.6
Hematuria	13 (100)	3 (75)	0.2
Complements			1.0
Low C3	5 (38)	2 (50)	
Low C3 and C4	3 (23)	0 (0)	
Normal C3 and C4	8 (62)	2 (50)	
Positive AI serologies and/or AD	13 (100)	0 (0)	–
AD	10 (77)	0 (0)	–
ANCA vasculitis	5 (50)	0 (0)	
Inflammatory bowel disease	1 (10)	0 (0)	
PMR	2 (20)	0 (0)	
AIHA	1 (10)	0 (0)	
MCTD	1 (10)	0 (0)	
APS	1 (10)	0 (0)	
AI serologies	12 (92)	0 (0)	–
ANA and/or double-stranded DNA	8 (62)	0 (0)	
ANCA			
Indeterminate	2 (15)	0 (0)	
Positive	6 (46)	0 (0)	
PR3	3 (23)	0 (0)	
MPO	2 (15)	0 (0)	
Unknown	1 (8)	0 (0)	
Anti-GBM antibody	0 (0)	0 (0)	
Other positive autoimmune serologies	4 (31)	0 (0)	

MCTD, mixed connective tissue disease; AIHA, autoimmune hemolytic anemia; PMR, polymyalgia rheumatica.

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Table 3. Clinical characteristics and demographics of individual patients with IRGN

Patient	Age/gender	Autoantibodies	Complement	Suspected infection source	AD	Other comorbidities
1	59/M	–	Normal	Cellulitis, HCV		Liver transplant, DM, HTN
2	62/M	+Beta-2 glycoprotein, +anti-cardiolipin	Normal	*E. coli* UTI, recurrent MSSA endocarditis, abscess on buttocks	Suspected APS	MGUS, low-grade MDS, CVA, HTN, paraplegia, neurogenic bladder, prosthetic AVR
3	30/M	–	Low C3	Prior HCV and fungemia	–	IVDU, EtOH abuse, asthma, dental caries
4	73/M	–	Low C3	Cellulitis, +ASO	–	HTN, CAD, MI, EtOH abuse
5	70/M	+ANA, +ANCA (MPO)	Normal	*S. pneumoniae* bacteremia and pneumonia	ANCA vasculitis	Bladder CA, COPD, ILD, CAD, DM, HTN
6	61/M	–	Normal	Unknown, resolved infection	Relapsing PMR	Bladder CA, HTN, chronic NSAID
7	70/M	–	Normal	PNA	–	AML, HTN
8	77/M	+ANA	Low C3	Sepsis	PMR/GCA	DM, HTN, CAD
9	57/M	+ANA, +F-actin IgG, +smooth muscle IgG	Low C3 and C4	Cellulitis	Statin-induced toxic versus AI myopathy	NASH/EtOH cirrhosis, HCC, poorly controlled DM, CAD, HTN, tobacco abuse
10	51/M	+ANCA (PR3)	Normal	MRSA tracheobronchitis	ANCA vasculitis	Hypothyroidism, recurrent aspiration
11	41/M	+ANCA (PR3)	Low C3 andC4	HIV on HAART, untreated HCV	ANCA vasculitis	Cirrhosis
12	80/M	+ANA, dsDNA ab+, +ANCA (MPO)	Normal	*E. faecalis* and *S. haemolyticus* endocarditis	AIHA and ANCA vasculitis	Prostate CA, poorly controlled DM, HTN
13	7/F	+ANA	Low C3	*S. pyogenes* bacteremia and UTI	–	Asthma
14	61/M	+ANCA (PR3), +RF	Low C3 and C4	*S. mitis* endocarditis	ANCA vasculitis	DM, HTN, dental caries, recent *H. pylori* infection
15	12/M	+ANA, +ANCA	Normal	MRSA cellulitis, MSSA bacteremia, osteomyelitis	Crohn's disease	–
16	63/F	+ANA, RNP, SM, Ro/SSA, lupus anticoagulant	Normal	Sepsis and *E. coli* UTI	MCTD	–
17	62/M	+ANA	Normal	*Staphylococcus* wound infection and osteomyelitis, HCV	–	DM, HTN, TIA, PVD, multiple amputations, SFA stent for non-healing wound

AIHA, autoimmune hemolytic anemia; AML, acute myelocytic leukemia, ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; APS, antiphospholipid syndrome; AVR, aortic valve replacement; CA, cancer; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; dsDNA ab, double-stranded DNA antibody; ESRD, end-stage renal disease; EtOH, ethanol; GCA, giant cell arteritis; HCC, hepatocellular carcinoma; HCV, hepatitis C; HD, hemodialysis; HTN, hypertension; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; MPO, myeloperoxidase; MGUS, monoclonal gammopathy of uncertain significance; NSAID, non-steroidal anti-inflammatory drug; PMR; polymyalgia rheumatica; PR3, proteinase-3; SFA, superior femoral artery; SLE, systemic lupus erythematosus; TIA, transient ischemic attack; UTI, urinary tract infection; HIV, human immunodeficiency virus; RF, rheumatoid factor; HAART, Highly Active Antiretroviral Therapy.

Table 4. Pathologic data of patients with IRGN at time of renal biopsy

	Patients, *n* (%) or intensity ± SD (patients, *n*)		
	IRGN with AI	IRGN without AI	*p* value
IF			
"Full-house" staining	3 (23)	1 (25)	1.0
Extra-glomerular staining	1 (8)	0 (0)	1.0
Average intensities			
IgA	1.1±0.9 (9)	0.8±1.0 (2)	0.5
IgG	1.5±1.2 (9)	1.0±1.4 (2)	0.6
IgM	0.8±0.7 (10)	1.0±1.2 (2)	0.7
C3	2.5±0.7 (13)	2.3±0.5 (4)	0.5
C1q	0.4±0.7 (4)	0.5±0.6 (2)	0.7
Kappa	1.5±0.9 (12)	1.0±0.8 (3)	0.3
Lambda	1.7±1.0 (12)	1.0±0.8 (3)	0.2
EM			
Tubuloreticular inclusions	1 (8)	0 (0)	1.0
Deposits			
Subepithelial deposits	12 (92)	3 (75)	0.4
Hump shaped	9 (69)	2 (50)	0.6
Mesangial	12 (92)	4 (100)	1.0
Subendothelial	6 (46)	3 (75)	0.6
LM			
Mesangial hypercellularity	9 (69)	4 (100)	0.5
Endocapillary hypercellularity	9 (69)	2 (50)	0.4
Exudative	7 (54)	1 (25)	0.6
Crescents			0.3
Cellular/fibrocellular			
Focal	7 (54)	1 (25)	
Diffuse	1 (8)	0 (0)	
Fibrous	0 (0)	0 (0)	
Fibrinoid necrosis	6 (46)	1 (25)	0.2
Membranoproliferative	4 (31)	2 (50)	0.6
Focal segmental glomerulosclerosis			0.6
Focal	4 (31)	2 (50)	
Diffuse	0 (0)	0 (0)	
Global glomerulosclerosis			0.4
Focal	8 (62)	2 (50)	
Diffuse	4 (31)	1 (25)	
Tubular atrophy and interstitial fibrosis			0.5
Mild	2 (15)	2 (50)	
Mild to moderate	3 (23)	0 (0)	
Moderate	1 (8)	1 (25)	
Moderate to severe	3 (23)	0 (0)	
Severe	1 (8)	1 (25)	

other serologies. Additional positive serologies included autoantibodies for beta-2 glycoprotein, anti-cardiolipin, lupus anticoagulant, F-actin IgG, smooth muscle IgG, rheumatoid factor, anti-nuclear ribonucleoprotein, anti-Smith antibody, and anti-Sjogren's syndrome A.

Pathologic Data

Pathologic features including IF, LM, and EM are presented in Table 4. More detailed pathologic data for AI and non-AI cases are provided in online supplementary Table 2. IF showed the most intense staining for C3 compared to all the immunoglobulins followed by IgG, kappa, and lambda showing the second most intense staining. Although there were no significant differences in IF staining between the groups, the AI cohort tended to show slightly stronger immunopositivity for IgA, IgG, kappa, and lambda. Both groups also showed similar frequency of full-house staining pattern, though only the AI group had 1 case with extra-glomerular staining involving tubular basement membranes by IgG and endothelial tubuloreticular

Table 5. Clinical outcomes of patients with IRGN

	Patients, *n* (%) or mean ± SD		
	IRGN with AI	IRGN without AI	*p* value
Average days to follow-up*	370±437	449±665	–
Complete recovery of renal function	2 (15)	1 (25)	–
Persistent renal dysfunction	3 (23)	1 (25)	–
ESRD	4 (31)	1 (25)	1.0
Average days to ESRD*	110±118	31	–
Death	6 (46)	1 (25)	0.6

ESRD, end-stage renal disease. * From time of biopsy.

inclusions. The AI and non-AI groups had no statistically significant differences in light microscopic findings in terms of both acute (e.g., mesangial and endocapillary hypercellularity, crescents) and chronic changes (e.g., global and segmental glomerulosclerosis, tubular atrophy, and interstitial fibrosis). Almost all of the biopsies showed some degree of activity except for 2 cases, which appeared to be in the resolving phase. None of the cases in the AI and non-AI cohorts had fibrous crescents. By EM, both groups showed no significant differences in the distribution of deposits or frequency of hump-shaped deposits (69% vs. 50%; $p = 0.6$).

35% ($N = 6$) were IgA dominant, of which 2 had cellulitis, 2 with staphylococcal infections, 1 with *Streptococcus pneumoniae*, and 1 unknown. 18% ($N = 3$) had endocarditis, all of which had full-house immune deposition by IF (1 with *Staphylococcus aureus*, 1 *Enterococcus faecalis* and *Streptococcus haemolyticus*, and 1 *Streptococcus mitis*), 12% ($N = 2$) had acute post-infectious GN (1 with *Staphylococcus aureus* and 1 *Streptococcus pyogenes*), 12% ($N = 2$) had HCV-associated MPGN, 6% ($N = 1$) had human immunodeficiency virus and HCV associated with full-house staining, 6% ($N = 1$) had *Escherichia coli*-related IRGN, and 12% ($N = 2$) were resolving GNs.

Follow-Up and Treatment

Follow-up data including treatment and clinical outcome are provided in Table 5 and in online supplementary Table 3. The mean days from time of biopsy to latest follow-up was 385 ± 461 for all IRGN cases. Eighteen percent of all IRGN had complete renal recovery, while 24% had persistent renal dysfunction. Five patients (29%) developed ESRD. Seven (41%) patients died (including 2 with ESRD): 2 from complications of malignancy, 1 from myocardial infarct, 1 from rhabdomyolysis, 1 from a possible pulmonary embolus, 1 from complications of cirrhosis, and 1 from multiple infections with vancomycin-resistant *Enterococcus*, *Clostridium difficile*, and *Klebsiella* bacteremia.

There were no significant differences in terms of treatment with immunosuppressive (77% in the AI and 67% in non-AI group; $p = 1.0$) or antibiotic/antiviral agents (85% in AI, 67% non-AI; $p = 0.5$). In addition, there were no significant differences in complete recovery, persistent renal dysfunction, ESRD, or mortality between the 2 groups.

All 3 cases that had underlying diabetic glomerulosclerosis (DGS) progressed to ESRD compared to 14% in those without DGS ($p = 0.01$). Patients with DGS also had worse tubulointerstitial scarring ($p = 0.03$) and global glomerulosclerosis ($p = 0.01$) but no significant differences in involvement by focal segmental glomerulosclerosis ($p = 0.5$). Of the 3 patients with DGS, 2 were from the AI group. There was a statistically significant relationship between ESRD and tubular atrophy and interstitial fibrosis ($p = 0.004$), presence of DGS ($p = 0.01$), MPGN ($p = 0.02$), and segmental sclerosis ($p = 0.03$).

Discussion

Herein, we report a cohort of patients with IRGN during a 7-year period to categorize cases with autoimmunity and identify their clinical and pathologic characteristics. Approximately 76% of the cases had evidence of either an AD and/or positive AI serologies, of which 92% had positive AI serologies and 77% had clinical evidence or history of an AD. Interestingly, while 30% had a prior diagnosis of AD, the remaining 70% did not have a history of AD and were either diagnosed or suspected of having an AD at the time of biopsy. The most common autoantibody identified was ANA (47%) followed by ANCA (35%) and serologies for APS such as lupus anticoagulant, beta-2 glycoprotein, or anti-cardiolipin autoantibodies (12%). Various autoantibodies

in the setting of IRGN have been identified in several studies and case reports [2]. The most identified autoantibody has been anti-IgG or rheumatoid factor, which has been reported in 15–32% of cases of acute post-streptococcal GN (APSGN) in one study but up to 89.2% of APSGN cases in another series [3, 7]. Other notable autoantibodies identified in the setting of IRGN include ANCA in 8–28% [8–11], anti-cardiolipin antibodies in 48% [12], anti-complement antibodies (such as anti-factor B [FB] in up to 91%, anti-C1q in 33–38%, and C3 nephritic factor in 20–64%) [13–18], and case reports of anti-dsDNA, antiphospholipid antibodies, and Coombs-positive AI hemolytic anemia including those with anti-I autoantibodies [19–21]. ANA was also detected in a significant proportion of cases with shunt nephritis (83%) [22]. In essence, the frequency of autoimmunity in IRGN is significant.

Growing evidence suggests that autoimmunity can be triggered by infections. ANA, Sm/RNP, anti-dsDNA, anti-heart, anti-smooth muscle, anti-mitochondrial, antithyroid, ANCA, and antiphospholipid antibodies, among other antibodies have been identified in the setting of various infections [4, 23–28]. Animal models of SLE and APS have demonstrated that viruses can trigger the production of autoantibodies [24, 29]. In a study of 88 non-AI patients with infections, 39% had at least 2 autoantibodies identified, the most common of which were antibodies to constituents involved in coagulation such as anti-annexin V, anti-prothrombin (PT), and antiphospholipid. Other commonly identified antibodies also included ANA, anti-*Saccharomyces cerevisiae* (ASCA), and anti-laminin. Elevated titers to annexin V and PT most often had viral, parasitic, and rickettsial infections (annexin V 60.9%, 47.1%, and 57.1%; PT 69.6%, 23.5%, 28.6%, respectively), while those with anti-ASCA and ANA were more prevalent in bacterial and viral infections (ASCA 22% and 26.1%; ANA 20% and 21.7%, respectively) [30]. In our cohort, we did not observe any difference in the type of autoantibodies in those with viral versus bacterial infections. That said, most of the infections were bacterial in our cohort with only a minority of viral infections and none with any known parasitic infection, thus limiting the ability to detect any true differences among type of infections.

Infections can trigger autoimmunity through multiple mechanisms including molecular mimicry, infection-induced changes in epitope conformation (e.g., leading to unmasking of previously sequestered components), antigen modification (e.g., formation of neoepitopes secondary to bacterial-induced alterations), and epitope spreading [1, 2]. For example, anti-IgG reactivity, which has been identified most in IRGN during the early phase of the disease, may be a result of autoantigenic modification through desialization of Ig by streptococcal neuraminidase [31, 32]. Defects in immune regulation are also well documented in both infection and autoimmunity, and an underlying genetic predisposition may play a role. Rodriguez-Iturbe et al. [33] reported a higher rate of APSGN in siblings compared to the general population in epidemics (38% vs. 5–28%). HLA-DP alleles, HLA-DPA1*02022 and DPB1*0501, ($p < 0.0001$ and $p < 0.0005$, respectively) as well as HLA-DRB1* 03011 and DRB1*1105 ($p = 0.00025$ and $p = 0.0097$, respectively) were found to be significantly increased in patients with APSGN [34, 35]. HLA-DRw4 was also discovered at a higher frequency in these patients ($p = 0.05$) [36]. These findings suggest genetic factors, particularly those involved with HLA-DR and DP [37], may increase the likelihood of developing IRGN in infection and could provide a potential link to an AI association. Polymorphisms of major histocompatibility complex class I and II genes are strongly associated with AD susceptibility, and it is major histocompatibility complex alone that is responsible for 30% of the genetic heritability for most ADs [38]. HLA-D genes, notably DR and DQ, have a strong association with almost all ADs [39]. Specifically, HLA-DRB1 alleles have been associated with increased risk factor for SLE, multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis, which has also been linked with HLA-DRw4 [38, 40–42]. HLA-DPB1 has been reported in various diseases including myasthenia gravis, Grave's disease, Takayasu's arteritis, celiac disease, juvenile arthritis, and primary biliary cirrhosis [34]. Of note, ANCA, which was one of the most common autoantibodies identified in our cohort, has been associated with HLA-DP and DQ variants [43, 44].

Similar to previous studies of IRGN in which hypocomplementemia is present in 35–85% [9, 45], our cohort demonstrated hypocomplementemia in 41% with similar frequency in both AI and non-AI group. Follow-up complement levels were available for 1 patient with initially low C3 that normalized within 2 months. Autoimmunity in alternative complement pathway (AP) dysregulation is of particular interest because a substantial proportion of cases with IRGN demonstrate not only mutations in complement genes but also a high frequency of autoantibodies against AP proteins such as C3NeF (20–64%) and anti-FB [13, 14, 17, 18]. Few reports and small cohort studies have also demonstrated normalization of the C3 levels upon disappearance of the anti-complement antibodies, suggesting that autoantibodies to complement enhance AP activation [13, 14]. Interestingly, a study by Chauvet et al. [13] identified anti-FB in 91% of children with APSGN

versus only 14% in those with C3 glomerulopathy (C3GN), indicating that the mechanism of AP activation may be different for C3GN and IRGN. Given the pathologic overlap between IRGN and C3GN and documented persistent IRGN progressing to C3GN, it seems dysregulation of AP due to autoimmunity likely has a central role in the pathogenesis of IRGN [46]. It is interesting to note that although there were no differences in frequency of low C3 between AI and non-AI group, low C4 was identified in only the AI cohort. Several studies have demonstrated an association of underlying C4 deficiency with increased susceptibility to infection and AD [47, 48]. That said, none of the cases with low C4 in the AI cohort had a documented history of decreased C4 prior to the diagnosis of IRGN.

Our cohort, which mostly comprised patients older than 50 years, showed similar biopsy and clinical findings to previous studies of IRGN in adults and the elderly. Similar to the study by Nasr et al. [10], many in our cohort were immunocompromised, with DM in a significant proportion (41% vs. 49%) but slightly more patients with malignancies (35% vs. 14%) and alcoholism or substance abuse (18% vs. 4%). Our cohort also showed the same common sites of infections including skin, respiratory and urinary tract, as well as endocarditis, sepsis, and osteomyelitis. Patients with DGS presented with more tubulointerstitial scarring and global glomerulosclerosis and were more likely to progress toward ESRD, correlating with prior studies showing worse renal prognosis in those with underlying DGS [10, 45]. There was also a direct correlation between ESRD and tubulointerstitial scarring, presence of MPGN pattern, and segmental sclerosis.

Our study has several limitations in that it is a single-center study in addition to aspects related to its retrospective nature including small sample size, variable treatment regimens, and lack of complete available clinical and laboratory data at presentation and follow-up. In addition, we do not know how long the autoantibodies were present prior to presentation and whether the infection itself led to autoantibody presence or if the autoantibodies were present for some time. Lastly, none of the patients had serologies for autoantibodies to complement or genetic analysis performed to further analyze the presence or absence of complement abnormalities or mutations implicated in autoimmunity.

In conclusion, AI manifestations are common in IRGN. Most of the cases had either positive AI serologies or clinical evidence or history of an AD. The most common autoantibody detected was ANA followed by ANCA and autoantibodies associated with APS. The study is not sufficiently powered to determine any significance but demonstrates the frequency with which AI features occur in IRGN. More studies are needed to understand the association of autoimmunity with IRGN and what the optimal management should be.

Acknowledgments

The authors are grateful to Karen Vanderbilt and Tracy Fontaine-Matteson for their excellent technical support.

Statement of Ethics

This research was performed under approval of the Research Subjects Review Board at University of Rochester (STUDY00007310), and all ethical principles and guidelines for the protection of human subjects were followed. This study has been granted an exemption from requiring written informed consent by the Research Subjects Review Board at University of Rochester.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

Author Contributions

Hae Yoon Grace Choung conceptualized, collected data, performed statistical analysis, and wrote the first draft of the manuscript. Hae Yoon Grace Choung and Rickinder Grewal performed formal analysis, wrote the review, and made revisions. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary materials. Further inquiries can be directed to the corresponding author.

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