Clinical Kidney Journal, 2023, vol. 16, no. 11, 1974–1979

https://doi.org/10.1093/ckj/sfad203
Advance Access Publication Date: 25 August 2023
Original Article

ORIGINAL ARTICLE

Clinical and pathological characteristics in elderly patients with IgA nephropathy

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ABSTRACT

Background. Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis, with highly variable manifestations. Although the peak incidence of IgAN is in young adults, the diagnosis among elderly people is increasing. Here we explored the effect of aging on IgAN features, as well as cellular senescence in the kidney of IgAN.

Methods. A total of 910 patients with IgAN were enrolled, which contained 182 individuals in each age stage (aged ≥60, 50–59, 40–49, 30–39 and 20–29 years). Clinical and pathological manifestations at the time of renal biopsy were compared. Additionally, 38 patients with IgAN (19 aged over or equal to 60 years and 19 aged below 60 years) were randomly selected for $p16^{INK4a}$ staining by immunohistochemistry. The percentage of $p16^{INK4a}$-positive cells in glomeruli, renal tubule and interstitium were separately quantified.

Results. Compared with young IgAN patients, elderly patients presented with higher levels of circulating IgA, uric acid and proteinuria, but lower estimated glomerular filtration rates (eGFR), as well as lower red blood cell counts, platelet counts and lymphocyte counts. Moreover, elderly IgAN patients showed higher incidence of hypertension, and lower incidence of prodromic infection. Regarding histological lesions in the kidney, young IgAN patients had higher degree of IgA and C3 deposits, while elderly IgAN patients had more severe Oxford-E lesions, but less severe Oxford-S lesions. The percentage of glomerular and tubular $p16^{INK4a}$-positive cells in elderly patients showed an increasing trend, but statistical significance was not reached. The percentage of $p16^{INK4a}$-positive nuclei in renal interstitium was positively associated with T score, while increased percentage of $p16^{INK4a}$-positive nuclei in renal tubule was associated with eGFR and 24-h urinary protein level.

Conclusion. In our IgAN cohort, elderly IgAN patients presented with some aging-related features, and both aging- and IgAN-induced pathological injury contributed to the kidney lesions in patients with IgAN.

Keywords: aging, cellular senescence, elderly IgAN, IgA nephropathy, $p16^{INK4a}$ staining

Received: 7.3.2023; Editorial decision: 21.8.2023

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common cause of primary glomerulonephritis globally, and it can occur at any age, although the second and third decades of life have been considered to be the most vulnerable life stages [1, 2]. The pathological features and clinical presentation of IgAN may vary greatly among patients and within the individual biopsy samples, ranging from isolated microhematuria and mild mesangial lesion to rapidly progressive glomerulonephritis and crescentic glomerulonephritis. Recent studies suggest that the incidence of IgAN is increasing among elderly people [3–5]. Compared with younger adults, older patients with IgAN exhibit higher rates of hypertension, poorer kidney function and higher degrees of tubulointerstitial fibrosis lesions [6]. Likewise, older patients with IgAN showed a faster decline of kidney function and greater mortality [7]. However, most of the data in these studies were obtained from small series of patients in observational studies [8–10].

As we all know, kidneys receive approximately 20%–25% of the cardiac output, and are highly metabolic organs which are susceptible to the aging process [11, 12]. After 30 years of age, approximately 6000–6500 nephrons are lost every year due to nephrosclerosis, or more specifically glomerulosclerosis. Aging-related structural changes to the kidney are concomitant with clinical and functional changes. These may contribute to phenotypical difference of elderly IgAN patients.

Normal aging is a natural, progressive and inevitable cause of cellular senescence. Moreover, cellular senescence is a critical factor for the processes of kidney aging and kidney disease. Senescent cells remain viable and show upregulation of $p16^{INK4a}$ [13], which functions as an inhibitor of CDK4 and CDK6. $p16^{INK4A}$ has the capability to arrest cells in the G1-phase of the cell cycle and its probable physiological role is in the implementation of irreversible growth arrest termed cellular senescence, hence $p16^{INK4A}$ is a marker of cellular senescence [14].

In this study, we recruited a large group of adult patients with biopsy-proven IgAN from different life stages, to explore the effect of aging on clinical and pathological features, as well as cellular senescence in the kidney of IgAN.

MATERIALS AND METHODS

Participants

Focusing on elderly IgAN patients, we first enrolled all patients aged 60 years or older and diagnosed as IgAN between 1997 and 2017 in Peking University First Hospital, after excluding secondary disease, which included 182 elderly IgAN patients. Then IgAN patients aged 20–59 years old were divided into four groups (20–29 years group, 30–39 years group, 40–49 years group and 50–59 years group). Using simple random sampling, we selected an additional 182 patients in each of these groups. In total, 910 patients with IgAN were enrolled in our present study. These patients were classified into five groups according to the age at the time of kidney biopsy, including elderly IgAN group (aged 60 years or older), adults IgAN group 3 (aged 50–59 years), adults IgAN group 2 (aged 40–49 years), adults IgAN group 1 (aged 30–39 years) and young IgAN group (aged 20–29 years).

The diagnosis of IgAN depends on the demonstration of glomerular mesangial deposition of IgA by immunofluorescence as well as electron-dense materials by electron microscopy.

The study complied with the Declaration of Helsinki principles and was approved by the Peking University First ethics committees. Written informed consent was obtained from all participants.

Clinical and histological features

Clinical and histological information at the time of kidney biopsy, including age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), 24-h urinary protein quantity (24-h UP), serum creatinine, uric acid, circulating IgA, circulating complement C3, blood count tests (including white blood cells, neutrophils, lymphocyte, platelets and red blood cells), triglycerides, cholesterol, low-density lipoprotein, high-density lipoprotein, prodromic infection and gross hematuria, were collected from medical records. The estimated glomerular filtration rate (eGFR), calculated by the Modified Glomerular Filtration Rate Estimating Equation, was used for renal function evaluation [15]. High blood pressure was defined as SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg at rest, or a self-reported history of hypertension [16].

In renal biopsy samples, mesangial deposition of IgA, IgG, IgM and C3 was detected using immunofluorescence assay and evaluated on a scale from 0 to 4+. Histological lesions were graded according to the Oxford Classification (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, glomerulosclerosis; T, tubular atrophy and interstitial fibrosis; and C, cellular or fibrocellular crescents) by qualified pathologists [17, 18].

$p16^{INK4a}$ immunohistochemistry

Among the enrolled 182 patients aged $\geq$60 years, 19 patients were randomly selected for $p16^{INK4a}$ staining. Among patients in the young IgAN group, adult IgAN group 1, adult IgAN group 2 and adult IgAN group 3, four or five patients were randomly selected from each group, to form a group of 19 patients aged 20–59 years for $p16^{INK4a}$ staining. Briefly, 2-μm sections of paraffin embedded tissue were deparaffinized and hydrated. Antigen retrieval was performed in EDTA buffer (0.01 mM EDTA, pH 9.0) at 100°C for 2 min, followed by cooling for 20 min. Endogenous peroxidases were then blocked using 3% H_2O_2 solution, followed by blocking of nonspecific staining with 20% normal goat serum. Tissue sections were then incubated at 4°C overnight with antibody against $p16^{INK4a}$ (Santa Cruz Biotechnologies, Santa Cruz, CA, USA) and rinsed with phosphate-buffered saline, followed by incubation with the horseradish peroxidase–conjugated goat anti-mouse/rabbit IgG polymer (ZSGB-Bio, Beijing, China). Specifically, bound antibodies were detected using the DAB substrate kit (ZSGB-Bio, Beijing, China). The slides were counterstained with hematoxylin and mounted. To quantify $p16^{INK4a}$-positive cells, 10 high-power fields on each slide were observed and percentage of positive nuclei was assessed by a blind observer.

Statistical analysis

Statistical data analysis was performed using SPSS 26.0 software (Chicago, IL, USA). Quantitative variables are described as mean ± standard deviation with a normal distribution or medium and interquartile range (IQR) with non-normal distribution. Categorical variables are shown as absolute values and percentages. Parametric and nonparametric tests were chosen as appropriated for descriptive comparisons of continuous variables, and chi-squared tests were used for categorical

variables. A linear regression analysis was performed to examine the relationship between $p16^{INK4a}$ staining and IgAN-associated phenotypes. Two-sided $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics

The main baseline characteristics are shown in Table 1. Males (data are presented in order of: elderly IgAN group, adult IgAN group 3, adult IgAN group 2, adult IgAN group 1, young IgAN group) comprised nearly half of all the patients in each group (57.7%, 59.9%, 49.5%, 47.3%, 52.2%, $P = .143$). At the time of kidney biopsy, young patients had a high incidence of prodromic infection (18.1%, 17.6%, 18.1%, 25.3%, 33.0%, $P = .001$) and gross hematuria (29.1%, 18.7%, 17.6%, 27.5%, 33.5%, $P = .001$). Meanwhile, elderly patients more frequently had hypertension (79.1%, 58.8%, 57.7%, 39.6%, 25.3%, $P < .001$). With increasing age, red blood cell count got lower [3.77 (IQR 3.32–4.27), 4.12 (IQR 3.71–4.62), 4.16 (IQR 3.71–4.62), 4.39 (IQR 3.93–4.79), 4.31 (IQR 3.85–4.80), $P < .001$]; meanwhile platelet count [207.00 (IQR 167.50–259.50), 210.00 (IQR 173.00–259.00), 235.00 (IQR 192.25–280.75), 222.00 (IQR 187.00–260.00), 229.00 (IQR 194.75–275.00), $P = .001$] and lymphocyte number [1.51 (IQR 1.10–1.99), 1.80 (IQR 1.44–2.15), 1.70 (IQR 1.40–2.01), 1.72 (IQR 1.44–2.03), 1.81 (IQR 1.50–2.23), $P < .001$] remained relatively stable during middle age (20–59 years old) but fell in old age (60+ years).

The blood triglycerides levels in young patients with IgAN were the lowest [1.75 (IQR 1.29–2.53), 1.81 (IQR 1.31–2.55), 1.90 (IQR 1.25–2.79), 1.72 (IQR 1.20–2.61), 1.40 (IQR 0.98–1.93), $P < .001$], while blood high-density lipoprotein levels [1.00 (IQR 0.83–1.26), 0.95 (IQR 0.81–1.13), 0.99 (IQR 0.84–1.23), 1.02 (IQR 0.86–1.25), 1.10 (IQR 0.92–1.32), $P < .001$] tended to decrease with age among patients younger than 60 years old. Cholesterol also tended to increase with age, but this was not statistically significant. Serum urine acid was elevated with increasing age of IgAN patients [378.00 (IQR 319.75–452.50), 379.50 (IQR 294.75–457.00), 370.00 (IQR 298.00–449.50), 351.40 (IQR 294.00–447.00), 340.00 (IQR 269.75–416.75), $P = .023$]. Circulating IgA levels increased with age [3.44 (IQR 2.60–4.55), 3.30 (IQR 2.33–4.22), 3.07 (IQR 2.46–3.98), 3.00 (IQR 2.35–3.69), 3.04 (IQR 2.29–3.81, $P = .003$], while eGFR showed an opposite trend [46.14 (IQR 26.03–69.40), 60.08 (IQR 39.26–82.99), 64.47 (IQR 45.11–91.10), 82.10 (IQR 56.52–107.14), 102.90 (IQR 73.93–121.02), $P < .001$]. The 24-h UP differed significantly among different groups, with the elderly IgAN group having the highest level [1.87 (IQR 0.99–4.07), 1.15 (IQR 0.59–2.51), 1.55 (IQR 0.74–3.22), 0.99 (IQR 0.54–2.01), 1.13 (IQR 0.53–2.55), $P < .001$]. As for pathological features, young IgAN patients presented with a higher degree of IgA and C3 deposits in the mesangial area. The percentage of glomerular sclerosis differed significantly in different life-stage groups [7.75 (IQR 0.00–20.00), 9.76 (IQR 3.54–23.71), 13.64 (IQR 4.49–27.18), 9.38 (IQR 0.00–28.57), 4.61 (IQR 0.00–17.70), $P = .003$]. In addition, the higher the age, the higher the proportion of Oxford-E1 (40.1%, 24.7%, 22.5%, 24.2%, 20.9%, $P < .001$), but the opposite was found regarding Oxford-S1 lesions (37.9%, 46.2%, 61.5%, 56.6%, 61.0%, $P < .001$). While the prevalence of Oxford-T1/T2 lesions in IgAN patients showed an increasing trend with age among those younger than 50 years old, for those over 50 years old, the prevalence remained relatively stable (42.4%/13.2%, 33.7%/17.1%, 41.8%/14.8%, 29.7%/13.7%, 26.4%/12.1%, $P = .006$).

Cellular senescence marker $p16^{INK4a}$ staining in kidney biopsy of IgAN patients

Staining of $p16^{INK4a}$ in kidney tissue of 38 patients with IgAN was analyzed. The percentage of positive cells in glomeruli, renal tubule and interstitium were separately quantified (Fig. 1). The percentage of $p16^{INK4a}$-positive nuclei in renal interstitium was comparable between patients more than 60 years old and in the 20–59 years old groups [0.00 (IQR 0.00–0.22) vs 0.05 (IQR 0.00–0.23), $P = .773$]. The proportion of $p16^{INK4a}$-positive cells in the glomerular and tubular regions exhibited an upward trend among elderly patients when compared with young adults, although no statistical significance was found [glomeruli: 0.67 (IQR 0.00–1.25) vs 0.00 (IQR 0.00–0.94), $P = .154$; renal tubule: 0.28 (IQR 0.09–0.68) vs 0.09 (IQR 0.00–0.36), $P = .123$].

Next, we evaluated the correlation of $p16^{INK4a}$ staining in kidney with clinical and histological features in the subgroup of patients. Liner regression analyses showed that $p16^{INK4a}$-positive nuclei in renal interstitium was associated with T score [regression coefficient (β) 0.234, 95% confidence interval (CI) 0.056 to 0.412, $P = .012$], while increased percentage of $p16^{INK4a}$-positive nuclei in renal tubule was associated with decreased eGFR [regression coefficient (β) –0.014, 95% CI –0.023 to –0.004, $P = .007$] and 24-h UP [regression coefficient (β) –0.083, 95% CI –0.161 to –0.005, $P = .039$]. No significant correlation with clinical and histological features was found regarding the percentage of $p16^{INK4a}$-positive nuclei in glomeruli.

DISCUSSION

In the present single-center cohort study, including 910 patients, we compared elderly and younger adults with IgAN, focusing on difference in clinical features, histological lesions and cellular senescence in the kidney. We found that elderly IgAN patients showed a higher degree of more severe impaired renal function and chronic lesions, and renal tubular and interstitial cell senescence was associated with some manifestations of kidney injury in IgAN.

In our IgAN cohort, many clinical and pathological features differed between elderly and younger IgAN patients. Some phenotypes that differed between elderly and younger IgAN patients may be aging-associated changes. For example, the elderly patients had a higher degree of comorbidities, such as hypertension and malnutrition (including lymphocyte number decreasing and worse anemia), as well as higher circulating IgA levels, but less incidence of prodromic infection, which might be because of a gradually weakened immune system with aging. Several previous reports have also described that circulating IgA level was positively associated with aging [19–21]. Besides the above changes, age-induced alterations in lipid metabolism may also occur [22, 23]. Consistent with previous reports, we also observed higher levels of cholesterol and lower levels of high-density lipoprotein in elderly and adult IgAN patients, compared with young patients. In addition, more severe Oxford-E lesions were observed in our elderly IgAN patients. Aging is associated with microvascular lesions and endothelial cell dysfunction, which may result from an increase in inflammatory mediators such as angiotensin II (Ang II), monocyte chemoattractant protein-1 (MCP-1) and milk fat globule EGF factor 8 protein (MFG-E8) with aging [24]. We suspected that aging might be one of the contributors to more severe endocapillary active lesions observed in our elderly IgAN patients.

Table 1: The clinical and pathological manifestations of patients with IgAN in different life stages.

Parameters	Elderly IgAN group, N = 182	Adult IgAN group 3, N = 182	Adult IgAN group 2, N = 182	Adult IgAN group 1, N = 182	Young IgAN group, N = 182	P-value
Clinical features						
Gender (male), *n* (%)	105 (57.7)	109 (59.9)	90 (49.5)	86 (47.3)	95 (52.2)	.143[a]
Age (years)	64 (62–69)	54 (52–56)	45 (42–47)	34 (32–37)	25 (23–27)	<.001[b]
Prodromic infection (yes), *n* (%)	33 (18.1)	32 (17.6)	33 (18.1)	46 (25.3)	60 (33.0)	.001[a]
Gross hematuria (yes), *n* (%)	53 (29.1)	34 (18.7)	32 (17.6)	50 (27.5)	61 (33.5)	.001[a]
Hypertension (yes), *n* (%)	144 (79.1)	107 (58.8)	105 (57.7)	72 (39.6)	46 (25.3)	<.001[a]
WBC ($\times 10^9$/L)	6.46 (5.30–7.73)	6.78 (5.90–8.30)	6.70 (5.86–7.97)	7.01 (5.66–8.20)	6.50 (5.57–8.23)	.319[b]
RBC ($\times 10^{12}$/L)	3.77 (3.32–4.27)	4.12 (3.71–4.62)	4.16 (3.71–4.62)	4.39 (3.93–4.79)	4.31 (3.85–4.80)	<.001[b]
PLT ($\times 10^9$/L)	207.00 (167.50–259.50)	210.00 (173.00–259.00)	235.00 (192.25–280.75)	222.00 (187.00–260.00)	229.00 (194.75–275.00)	.001[b]
NE ($\times 10^9$/L)	4.26 (3.13–5.62)	4.20 (3.39–5.20)	4.33 (3.51–5.32)	4.50 (3.40–5.68)	4.08 (3.38–5.50)	.762[b]
LY ($\times 10^9$/L)	1.51 (1.10–1.99)	1.80 (1.44–2.15)	1.70 (1.40–2.01)	1.72 (1.44–2.03)	1.81 (1.50–2.23)	<0.001[b]
TG (mmol/L)	1.75 (1.29–2.53)	1.81 (1.31–2.55)	1.90 (1.25–2.79)	1.72 (1.20–2.61)	1.40 (0.98–1.93)	<.001[b]
CHO (mmol/L)	4.97 (4.23–5.81)	4.81 (3.98–5.65)	4.73 (3.90–5.71)	4.58 (3.93–5.44)	4.59 (4.03–5.50)	.123[b]
HDL (mmol/L)	1.00 (0.83–1.26)	0.95 (0.81–1.13)	0.99 (0.84–1.23)	1.02 (0.86–1.25)	1.10 (0.92–1.32)	<.001[b]
LDL (mmol/L)	2.97 (2.18–3.72)	2.62 (2.21–3.27)	2.65 (2.05–3.37)	2.65 (2.09–3.29)	2.79 (2.23–3.53)	.106[b]
cIgA (g/L)	3.44 (2.60–4.55)	3.30 (2.33–4.22)	3.07 (2.46–3.98)	3.00 (2.35–3.69)	3.04 (2.29–3.81)	.003[b]
cC3 (g/L)	0.99 (0.85–1.16)	0.99 (0.87–1.15)	0.96 (0.83–1.13)	0.99 (0.83–1.13)	0.97 (0.85–1.07)	.163[b]
UA (μmol/L)	378.00 (319.75–452.50)	379.50 (294.75–457.00)	370.00 (298.00–449.50)	351.40 (294.00–447.00)	340.00 (269.75–416.75)	.023[b]
eGFR (mL/min/1.73 m^2)	46.14 (26.03–69.40)	60.08 (39.26–82.99)	64.47 (45.11–91.10)	82.10 (56.52–107.14)	102.90 (73.93–121.02)	<.001[b]
24-h UP (g/24 h)	1.87 (0.99–4.07)	1.15 (0.59–2.51)	1.55 (0.74–3.22)	0.99 (0.54–2.01)	1.13 (0.53–2.55)	<.001[b]
Pathological features						
Global glomerulosclerosis (yes), (%)	7.75 (0.00–20.00)	9.76 (3.54–23.71)	13.64 (4.49–27.18)	9.38 (0.00–28.57)	4.61 (0.00–17.70)	.003[b]
M1	117 (64.3)	122 (67.0)	127 (69.8)	115 (63.2)	123 (67.6)	.684[a]
E1	73 (40.1)	45 (24.7)	41 (22.5)	44 (24.2)	38 (20.9)	<.001[a]
S1	69 (37.9)	84 (46.2)	112 (61.5)	103 (56.6)	111 (61.0)	<.001[a]
T1/T2	77 (42.3)/24 (13.2)	61 (33.7)/31 (17.1)	76 (41.8)/27 (14.8)	54 (29.7)/25 (13.7)	48 (26.4)/22 (12.1)	.006[a]
C1/C2	83 (45.6)/28 (15.4)	90 (49.7)/20 (11.0)	89 (48.9)/22 (12.1)	86 (47.3)/17 (9.3)	81 (44.5)/20 (11.0)	.742[a]
IgG (0/1+/2+/3+)	156 (85.8)/23 (12.6) /3 (1.6)/0 (0.0)	153 (84.0)/21 (11.5) /7 (3.9)/1 (0.6)	152 (83.5)/23 (12.6) /6 (3.3)/1 (0.6)	140 (76.9)/30 (16.5) /11 (6.0)/1 (0.6)	152 (84.0)/20 (11.0) /7 (3.9)/2 (1.1)	.578[a]
IgA (1+/2+/3+–4+)	6 (3.3)/52 (28.6) /124 (68.1)	2 (1.1)/59 (32.4) /121 (66.5)	3 (1.6)/39 (21.5) /140 (76.9)	3 (1.6)/31 (17.1) /148 (81.3)	2 (1.1)/39 (21.4) /141 (77.5)	.002[a]
IgM (0/1+/2+/3+)	87 (47.8)/58 (31.9) /34 (18.7)/3 (1.6)	70 (38.5)/74 (40.6) /36 (19.8)/2 (1.1)	72 (39.6)/69 (37.9) /38 (20.9)/3 (1.6)	56 (30.8)/75 (41.2) /48 (26.4)/3 (1.6)	69 (38.1)/66 (36.5) /42 (23.2)/4 (2.2)	.340[a]
C3 (0/1+/2+/3+–4+)	24 (13.2)/39 (21.4) /51 (28.0)/68 (37.4)	21 (11.5)/28 (15.4) /69 (37.9)/64 (35.2)	11 (6.0)/20 (11.0) /83 (45.6)/68 (37.4)	13 (7.2)/19 (10.4) /53 (29.1)/97 (53.3)	9 (4.9)/18 (9.9) /70 (38.5)/85 (46.7)	<.001[a]

Data are presented as *n* (%) or median (IQR).

[a]Chi-square test was used for comparison.

[b]Kruskal–Wallis test was used for comparison.

WBC: white blood cell count; RBC: red blood cell count; PLT: platelet count; NE: neutrophil count; LY: lymphocyte count; TG: triglycerides; CHO: cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; cIgA: circulating IgA; cC3: circulating complement C3; UA: uric acid.

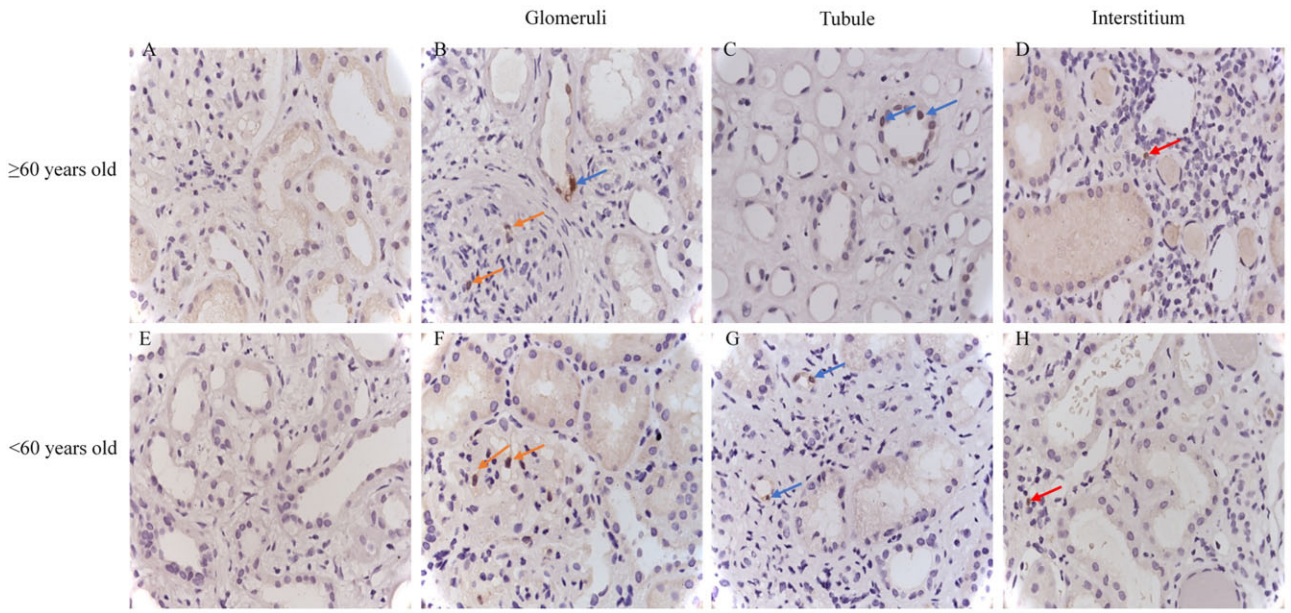

Figure 1: Representative images of $p16^{INK4a}$ staining in glomeruli, tubule and interstitium. Representative kidney $p16^{INK4a}$ staining of the elderly and young IgAN patients, including negative $p16^{INK4a}$ staining (**A**, **E**), as well as positive $p16^{INK4a}$ staining cells in renal glomeruli (**B**, **F**, orange arrows), tubule (**C**, **G**, blue arrows) and interstitium (**D**, **H**, red arrows).

IgAN has some characteristic features, including upper respiratory infection followed by gross hematuria in a short time, IgA-predominant glomerular deposition, which give rise to complement activation manifesting as complement C3 protein deposition in the mesangial area. In our IgAN cohort, these IgAN-associated features were more frequently observed in young IgAN patients. In previous observational studies conducted in South Korea and in our IgAN cohorts, Oxford-M1, Oxford-S1 and Oxford-T1/2, but not Oxford-E score, were significantly correlated with C3 deposition [25, 26]. Therefore, we speculated that the peculiar less severe chronic sclerotic lesions (Oxford-S score) in elderly patients might result from less magnitude of complement activation. Although the exact pathogenesis of IgAN is still unknown, it is widely considered to be an autoimmune disease, as evidenced by the contribution of anti-glycan IgG or IgA1 antibodies against aberrantly glycosylated IgA1 in IgAN, as well as the strong association of HLA loci with IgAN susceptibility [27–29]. Aging causes many biological changes in the immune system and leads to immunity decrease [30, 31]. Compared with young IgAN patients, the acute clinical symptoms and pathological active renal lesions were less in elderly IgAN patients. We suspected that this might be because of a weakened immune system caused by aging.

It is well known that the percentage of global glomerulosclerosis increases with age [32]. However, in our present IgAN cohort, the highest percentage of globally sclerotic glomeruli was observed in IgAN patients aged 40–49 years, but not in the elderly IgAN group. This finding suggested that glomerulosclerosis in IgAN patients may result not only from aging but also from IgAN-induced kidney injury. Our results of $p16^{INK4a}$ staining are also in line with this. In IgAN patients, the presence of $p16^{INK4a}$, a marker indicating cellular senescence, was found to be more pronounced in the renal glomeruli and tubules of elderly patients. However, due to a limited number of patients recruited for $p16^{INK4a}$ staining, statistical significance was not achieved. The expression of $p16^{INK4a}$ in renal tubule and interstitium was associated with some morphological and functional indices reflecting kidney injury, including eGFR, 24-h UP and Oxford-T scores, which implied that IgAN also contributed to cellular senescence in the injured kidney.

In conclusion, in our present IgAN cohort, elderly IgAN patients presented with some aging-related features, and both aging- and IgAN-induced pathological injury contributed to the kidney lesions in patients with IgAN.

FUNDING

This project was supported by grants from the National High Level Hospital Clinical Research Funding (Interdisciplinary Clinical Research Project of Peking University First Hospital, 2022CR39), the National Key Research and Development Program of China (2020YFC2005003) and the National Science Foundation of China (81970598, 82170710, 82270740).

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article itself.

CONFLICT OF INTEREST STATEMENT

All the authors declare no conflicts of interest.

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Received: 7.3.2023; Editorial decision: 21.8.2023