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RESEARCH

The renal histopathology of nonproteinuric kidney impairment: a three center experience

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Abstract

Proteinuria is a biomarker of kidney injury that typically results from glomerular and/or tubulointerstitial disease. Whereas kidney impairment with normal urinary protein excretion is usually less focused and understudied. We conducted a retrospective review of the renal histopathology of the patients with variable degrees of unexplained renal insufficiency but with normal range proteinuria between 2014 and 2024 of three university teaching hospitals in Shenzhen city of Southern China. Patients with kidney dysfunction of undetermined or uncertain etiology and with normal urinary protein excretion (defined by a 24hr urinary protein excretion < 150 mg or spot urinary protein to creatinine ratio [PCR] < 150 mg/g) were enrolled and analyzed. In a total of 2405 patients, 53 (2.2%) fulfilled the inclusion criteria (male/female 40/13, age 47.3 ± 14.3 years) with a mean eGFR of 46.6 ± 16.8 ml/min per 1.73 m^2. Glomerular disease (GD) was the most frequent pathological finding identified in 23 (43.4%) patients, while 19 (35.8%) cases showed tubulointerstitial disease (TID) and 11 (20.8%) patients exhibited small vascular disease (SVD). Patients in the TID had the lowest mean eGFR and the highest numerical 24hr urinary protein excretion among the three groups. The incidence of acute kidney injury was significantly higher in TID than in other two groups. The patients in the SVD group had the highest fraction of underlying hypertension. Kidney dysfunction with normal range proteinuria may be related with, in descending order of probablity, glomerular, tubulointerstitial and small vascular diseases. Renal biopsies were proved useful in informing therapeutic choice, long-term management and in predicting prognosis in this setting.

Keywords Kidney biopsy · Proteinuria · Glomerular disease · Tubulointerstitial disease · Small vascular disease

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Introduction

The development of percutaneous renal biopsy (PRB), pioneered by Iversen and Brun in 1951, has profoundly impacted the practice of Nephrology and altered the landscape of renal medicine [1]. Nowadays, kidney biopsy remains essential and irreplaceable in the management of patients with unexplained or unremitting AKI, chronic kidney disease (CKD), and those with kidney allograft dysfunction [2]. Being an invasive procedure however, PRB is used with caution clinically to evaluate the status, activity, and ideally pathophysiology, of kidney injury to inform prognosis and clinical decision. Although a universal guideline has not been found, renal insufficiency, hematuria and excessive proteinuria have routinely served as common indications of kidney biopsy [2, 3]. Proteinuria is a biomarker of renal injury and a driver of CKD as well, which typically arises from glomerular and/or tubulointerstitial disease [4]. A persistently high level of proteinuria associates with irreversible parenchymal damage predicting adverse renal and cardiovascular outcomes [5, 6]. Yet a normal urinary protein excretion does not exclude kidney damage either in its incipient or advanced disease stage [7–11].We herein set to investigate the renal histopathological profile in a group of patients from three tertiary institutions with varying degrees of unexplained renal dysfunction in the absence of overt proteinuria, aiming to provide some experience, reference and insight in the judgement and management in this setting.

Materials and methods

Patient selection and inclusion criteria

All renal biopsies performed between January 2014 and March 2024 in the Nephrology departments of three teaching hospitals in Shenzhen city were reviewed retrospectively. The renal pathological databases were searched to identify any cases meeting the following 3 inclusion criteria: (1) native renal biopsy, (2) normal range of urinary protein (defined by a 24hr urinary protein [24hr-UPr] of less than 150 mg, or spot urine protein to creatinine ratio [PCR] < 150 mg/g [if a 24hr-UPr is unavailable], which is in consistent with the A1 category of proteinuria adopted by KDIGO guideline [12]), and (3) undetermined etiology of kidney functional impairment (using the lowest estimated glomerular filtration rate [eGFR, calculated by 4 index CKD-EPI equation for Chinese: $175 \times (Cr_{Jaffe})^{-1.234} \times (Age)^{-0.179} (\times 0.79$ if female) [13]] of less than 80 ml/min per 1.73 m^2(age- and gender-matched mean eGFR value in the general population) within 1 weeks before biopsy. The exclusion criteria are: (1) younger than 18 years of age, and (2) use of glucocorticoid, immunosuppressive or immunomodulating agent currently or within 6 months before biopsy.

Evaluation of the renal biopsy specimens

All specimens were processed for light microscopy (LM), immunofluorescence (IF) and electronic microscopy (EM). Paraffin sections were cut in 2.5 μm of thickness and stained with hematoxylin and eosin, Masson trichrome, periodic acid–Schiff, Jones methenamine silver, and Congo Red. Snap-frozen fresh tissues cut in 3.5 μm were stained with fluorescein-tagged rabbit anti-human polyclonal antibodies for evaluation of IgG, IgA, IgM, C3, C1q, fibrinogen, and κ and λ light chains. EM samples were processed and assessed per standardized protocol [14].

All candidate biopsies were reevaluated by two pathologists and two nephrologists independent of one another. The following consensus criteria were adopted to describe the pathological changes. Glomerular minor change (GMC) is define as: (1) weak or mild degree focal or segmental mesangial expansion or proliferation, (2) negative or weak IF stain (trace or 1 + intensity on a scale of 0–3), (3) absence or insignificant change in the tubulointerstitial area (< 5–10%), and (4) absence of EM changes characteristic or specific to a known entity (e.g., thrombotic microangiopathy, or monoclonal immunoglobulin deposition disease, etc.). Immunoglobulin A Nephropathy (IgAN) is diagnosed according to the 2016 updated Oxford classification [15]. The diagnosis of diabetic kidney disease (DKD) is made in the light of a history of diabetes mellitus(DM) and in the presence of one or more of the following 4 histopathological changes, given other entity that may potentially lead to similar abnormality is otherwise excluded: (1) glomerular basement membrane (GBM) thickening (> 395 nm in female, and > 430 nm in male), (2) mesangial expansion, (3) arteriolar hyalinosis, and (4) Kimmelstiel-Wilson(K-W) nodule or capsular drop[16, 17]. Small vascular disease (SVD) is defined as the presence of one or more following small arterial or arteriolar changes without significant glomerular or tubulointerstitial lesion: (1) vessel wall thickening or sclerosis, (2) narrowing of vessel lumen, (3) hyalinosis. Tubular interstitial disease (TID) is defined by the presence of one or more following three features: (1) tubular cell degeneration, necrosis, or atrophy, (2) inflammatory hypercellularity and edema of the interstitium, and (3) interstitial fibrosis in the absence of significant glomerular or small arterial disease. The degree of podocyte foot process effacement (PFPE) observed on EM was graded into 3 classes: segmental, < 50%; major, 50–90%; and extensive, > 90% of the podocytic area. After the pathologists and nephrologists reviewed the cases independently,

the histopathologies were discussed and ascertained. If there had been any dissention, discussions were held to reach a consensus. The final renal pathological category was classified according to the major histological changes that deemed contributing most to its kidney dysfunction.

Measurement of urinary protein and creatinine

Urinary protein and albumin level were measured by using the turbidimetry method, serum and urinary creatinine concentration by the Jaffe method. All measurements were carried out on chemical autoanalyzers in the central clinical laboratories of the three hospitals.

Statistics analysis

Results are expressed using mean ± SD or median or interquartile ranges as appropriate. To assess significance, the categorical data were compared between groups with the χ^2 test or Fisher's exact test. The quantitative data were compared with *t* tests or ANOVA. All tests were two-tailed, a *p* value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26.0 for Windows (SPSS, Chicago, IL, USA).

Outcomes

A total of 2405 ultrasound-guided native PRBs were performed during the study period in the three institutions (the university of Hong Kong-Shenzhen Hospital, Shenzhen University General Hospital, and Shenzhen Hospital of Southern Medical University). 53 patients fulfilled the inclusion criteria which accounted for 2.8%, 1.7% and 1.23% of PRB patients of the respective three centers (the rates between the first and the third unit had a significant difference only, $p = 0.015$). The 53 cases comprised 40 male and 13 female with a mean age of 47.3 ± 14.3 years. 17 (32.1%) and 15 (28.3%) patients had background hypertension (HT) and DM respectively, and nine (15.5%) had intercurrent HT and DM. Seven patients had a history of gout, and one patient was diagnosed monoclonal gammopathy of undetermined significance (MGUS) before biopsy. 12 out of 53 patients were taking an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for durations of one month to four years. No patient was using sodium glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase 4 (DDP4) inhibitor, or mineralocorticoid receptor antagonist before renal biopsy. The flow chart of patient enrollment

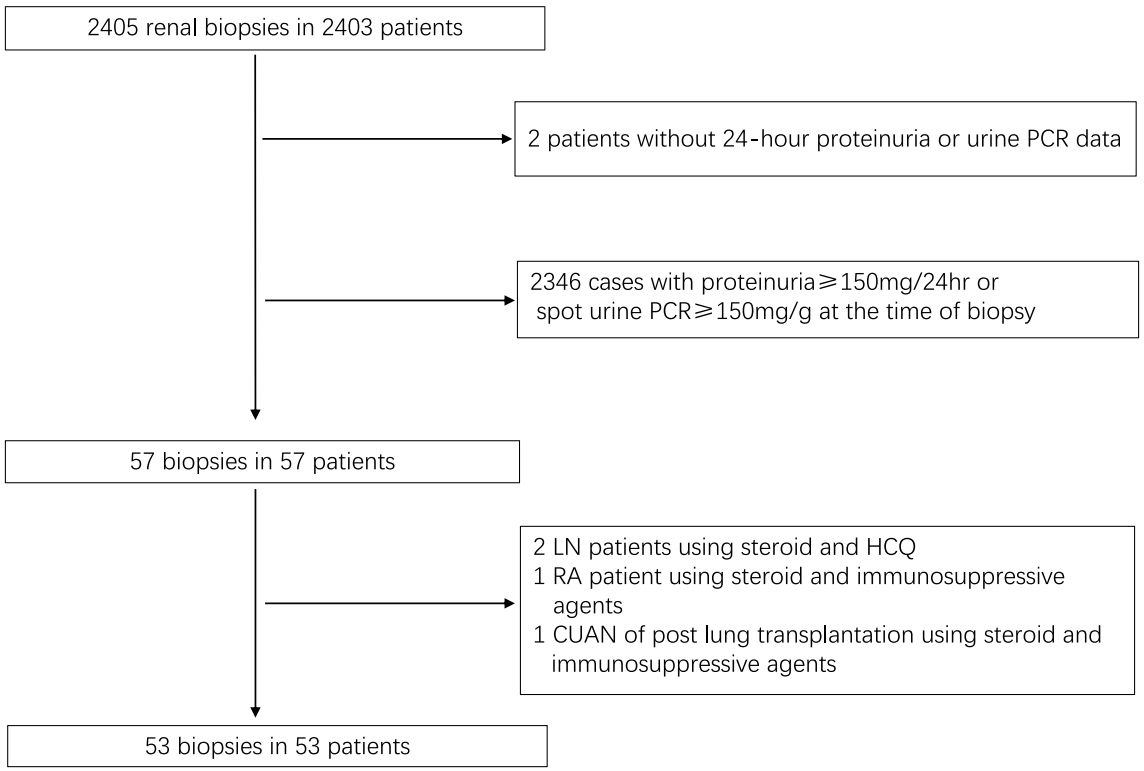

Fig. 1 Flow chart of patient recruitment (PCR, protein to creatinine ratio; LN, lupus nephritis; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; CUAN, chronic urate acid nephropathy.)

is shown in Fig. 1, and the demographic and clinical characteristics of the 53 patients are shown in Table 1. The average peak serum creatinine level within 1 week before biopsy was 168.6 ± 108.9 μmol/l, coupling a trough eGFR of 46.6 ± 16.8 ml/min per 1.73 m^2. The 24hr-UPr and 24hr urinary albumin levels were 101.3 ± 28.8 mg (Table 1) and 13.5 mg (3.3, 46.8) respectively. Nearly three-fourth (39/53, 73.6%) of patients had an eGFR < 60 ml/min per 1.73 m^2 (range 6.7–59.5). The rest 14 (26.4%) patients had a reduced eGFR (range 60.8–77.3 ml/min per 1.73 m^2) comparing to gender- and age-matched normal population [18]. Microscopic urinary erythrocyte were present in only five of the 53 patients (4 in the GD group, and 1 in the SVD group, Table 2).

The kidney histopathology of the 53 patients can be classified into three categories: GD, TID and SVD. GD was the most frequent pathological change identified in 23 patients (43.4%); 19 patients (35.8%) displayed TID, and 11 patients (20.8%) exhibited SVD as the major pathological impairment (Fig. 2a–c, Table 2). In the GD group, eight patients displayed GMC, seven had IgAN (2 M0E0S0T0C0, 1 M0E0S1T0C0, 1 M1E0S1T0C0 and 3 M1E0S1T0C1), three revealed DKD, two cases had MPGN, one patient with FSGS and 1 with Immune complex mediated glomerulonephritis. And, there was one case of diffuse proliferative glomerular nephritis (DPGN) secondary to cryoglobulinemia (patient no. 6, Table 2). In the TID group, 14 of the 19 patients observed acute tubulointerstitial injury (2 had underlying IgAN, patient nos. 31,42), 5 patients were diagnosed chronic tubulointerstitial disease (1 case with concurrent DKD, patient no.40). In the SVD group, the renal impairment of six patients were attributed to HT, one patient was linked to DM, and two patients to concurrent HT and DM. Patients in TID had the lowest mean eGFR and the highest numerical 24hr-UPr among the three groups (Fig. 3a, b, Table 3). Ten of the 53 patients presented with AKI (2012 KDIGO definition) within two weeks before renal biopsy, of whom nine were in the TID group, the other one was in the GD group (the case with DPGN). The incidence of AKI was significantly higher in the TID group than in the GD ($p = 0.002$) and the SVD group ($p = 0.011$). Patients in SVD group had a higher rate of underling HT versus the TID group ($p = 0.004$) and GD group ($p = 0.066$). The pathological characteristics of the 53 patients are shown in Table 2.

Table 1 Basic characteristics of the 53 patients.

Items	Values
Gender (M/F)	40/13
Age (year)	47.3 ± 14.3
Serum creatinine (μmol/L)	168.6 ± 108.9
eGFR (ml/min -1.73m^2)	46.6 ± 16.8
24hr proteinuria (mg)	101.3 ± 28.8
24hr albuminuria (mg)	13.5 (3.3, 46.8)
Hematuria (n/%)	5/9.43
Duration of renal dysfunction 1 days to 6 yrs	
Comorbidities (n/%)	
HT	17/32.1
DM	15/28.3
HT + DM	8/15.1
Gout	7/13.2
MGUS	1/1.9

HT Hypertension; *DM* Diabetes mellitus; *MGUS* Monoclonal gammopathy of undetermined significance.

Discussion

Proteinuria, along with hematuria and serum creatinine and cystatin C, represents the essential biomarker of kidney injury. 24 hr urine proteinuria has been widely accepted as gold standard in urinary protein evaluation, providing accurate sample collection had been made. Spot urine PCR and albumin-creatinine ratio (ACR) have very good correlation with timed urine protein, while its diagnostic performance could be compromised in high-level proteinuria (> 3.0–3.5 g/day) [19, 20] or in low urinary creatinine excretion[21], which may result in under- or over-estimate daily urine protein respectively. Pathological proteinuria typically results from disruption of glomerular filtration barrier and/or the impairment of the renal tubular resorptive function. It is estimated that kidneys may reabsorb as much 3.2 g of albumin and 9.6 g of low molecular protein (given a sieving coefficient of 0.00062 and 0.987 respectively) daily in a normal adult [22]. Under pathological conditions, not including overflow proteinuria as in multiple myeloma, abnormal urinary protein occurs in either of the two situations: (1) glomerular filtration barrier damage leading to excessive protein in the primary urine exceeding the tubular resorption reserve, and (2) impairment of resorptive capability owing to functional or structural damage of the tubule. An extreme example of the latter is Dent disease, in which mutations of the *ClCN5* or *OCRL* gene result in defective membrane traffic of apical megalin and cubilin receptors in the tubular epithelial cells to cause the marked proteinuria consisting of both low molecular protein and albumin [23]. The protein in the primary urine is mainly reabsorbed via megalin and cubilin of the renal tubules, with around 71% albumin retrieved in the proximal tubule and 26% in the distal nephron according to animal model [22]. As such, it seems sensible to suggest that the 2.2% of non-proteinuric patients in our cohort may have preserved tubular resorptive function to trade off the proteinuric leak by glomerular injury. Similar instances had been documented in a number of glomerular or non-glomerular entities [7, 9, 10, 24–27],

Table 2 The patient characteristics, eGFR, urinary protein and major pathological change of the 53 patients.

No	Gender (M/F)	Age (year)	Category	SCr (μmol/L)	AKI	eGFR (ml/min-1.73 m^2)	24hr-Upr (mg)	24hr-UAE (mg)	Concurrent disease	
									HT	DM
1	M	42	GD	120.3	−	61.3	58.9	3.4	+	+
2	M	31	GD	124	−	62.3	66.7	5.2	−	−
3	M	45	GD	115.8	−	63.4	96.3	20.7	+	−
4	M	42	GD	123	−	59.6	61.7	1.5	−	−
5	F	29	GD	151	−	39.1	46.9	1.0	−	−
6	F	68	GD	177	+	27.9	113.6	50.2	+	+
7	M	35	GD	123	−	62.0	64.2	1.0	−	−
8▲	M	42	GD	114	−	65.5	129.0	66	+	−
9▲	M	41	GD	151	−	46.5	50.9	5.1	−	−
10	M	48	GD	149	−	46.0	98.2	12.2	+	+
11	M	38	GD	121	−	61.9	144.4	101	−	−
12▲	F	37	GD	87	−	73.9	120.0	69.3	−	−
13●	M	81	GD	161	−	38.0	83.6	13.9	+	+
14	F	56	GD	100	−	57.8	120.0	69.3	−	−
15	M	31	GD	114	−	73.4	87.7	1.7	−	−
16	F	58	GD	133	−	38.0	113.31	56.8	+	−
17	M	36	GD	172	−	35.5	142.97	70.5	−	−
18	M	41	GD	123	−	62.4	126	NA	−	-
19	F	62	GD	134	−	32.5	73.2	NA	−	+
20▲	M	58	GD	112	−	62	142.5	NA	−	−
21	M	61	GD	120	−	55.9	143.25	NA	−	−
22	F	42	GD	100.7	−	59.3	141.5	NA	+	−
23	M	55	GD	156.8	−	42.11	90.39	NA	−	+
24	M	64	TID	122	−	53.6	110	NA	−	+
25	M	40	TID	125.2	−	58.8	71.82	NA	−	−
26	M	26	TID	260	+	25.8	100.1	NA	−	−
27	M	38	TID	225	+	28.8	129.0	22.9	−	−
28	M	50	TID	141.5	−	48.6	92.9	0.7	−	−
29	M	62	TID	187.5	+	33.1	118.7	18.3	−	−
30※	M	55	TID	124	−	56.3	NA	NA	−	−
31	F	21	TID	663	+	6.7	130.7	77	−	−
32◆	M	27	TID	112	−	72.4	130.1	1.3	−	−
33	M	64	TID	214	−	28.1	71.3	1	−	+
34	M	72	TID	216	+	27.2	59.2	8.2	+	+
35	M	63	TID	665	+	6.9	101.4	34.0	+	+
36	F	21	TID	286	−	18.8	130.4	13.2	−	−
37	M	46	TID	126	−	58.5	77.84	7.0	−	−
38	F	60	TID	161	+	29.7	149.78	29.3	+	−
39	M	22	TID	213	+	36.7	78	NA	−	−
40	M	66	TID	160	−	38.1	123.2	NA	−	+
41※	F	45	TID	239	+	24.7	NA	NA	−	−
42	M	33	TID	125.3	−	60.8	75.94	NA	−	−
43	M	49	SVD	191	−	33.7	113.0	NA	+	−
44	M	33	SVD	119	−	64.9	80.77	NA	+	−
45	M	60	SVD	139	−	48.1	118.0	13.8	+	+
46	F	47	SVD	141	−	39.0	124.4	45.7	+	−
47▲	M	34	SVD	152	−	47.7	118.68	39.2	+	−

Table 2 (continued)

No	Gender (M/F)	Age (year)	Category	SCr (μmol/L)	AKI	eGFR (ml/min-1.73 m^2)	24hr-Upr (mg)	24hr-UAE (mg)	Concurrent disease	
									HT	DM
48	M	40	SVD	107	−	71.4	92.4	2.9	+	−
49	M	63	SVD	261	−	21.9	71.84	4.4	−	+
50	M	52	SVD	115	−	47.2	79.25	5.3	−	−
51※	F	60	SVD	95	−	52.2	NA	NA	−	−
52※	M	57	SVD	128	−	53.2	NA	NA	+	+
53※	M	59	SVD	138	−	47.9	NA	NA	+	−

No	Pathology							
	Major diagnosis	Glom/sGlom	IF	ICI	TA/IFib	SAWT	SAH	PFPE
1	GMC	11/0	IgA1 +, IgM 1 +,C1q ±	Neg.	Focal/Neg.	Neg.	Neg.	Segmental
2	IgAN(M0E0S0T0C0)	52/4	IgA2-3 +, IgM 1 +, C3 ±	< 5%	Neg./Neg.	Neg.	Neg.	Major
3	GMC	16/0	IgM ±	±	Neg./Neg.	Isolate	Neg.	Segmental
4	GMC	41/3	Neg.	±	Focal/Neg.	Neg.	Neg.	Segmental
5	GMC	8/2	C3 ± -1 +, IgM ±,C1q ±	±	Focal/Neg.	Neg.	Neg.	Major
6	DPGN(CryoGN)	17/1	IgG 1 +,IgM 2 +,C3 ±,C1q 1 +,κ 1–2 +,λ 1 +	Focal	10%/Focal	Present	Neg.	Major
7	GMC	45/8	IgA 1 +, IgM ±	Neg.	Neg./Neg.	Present	Present	Diffuse
8▲	IgAN(M0E0S0T0C0)	16/0	IgA 1–2 +,C3 ± -1 +,IgM 1 +	< 3%	< 3%/ < 3%	Isolate	Neg.	Major
9▲	GMC	39/7	Neg.	5%	10%/Focal	Neg.	Neg.	NA
10	DKD	13/6	Neg.	±	10%/ < 10%	Present	Present	Segmental
11	GMC	16/3	IgA ± -1 +	Neg.	< 5%/ < 5%	Isolate	Neg.	Segmental
12▲	IgAN(M0E0S1T0C0)	15/2	IgA 3 +, C3 1–2 +, IgM ± -1 +	±	5%/5%	Neg.	Neg.	Major
13●	GMC	26/2	Neg.	±	< 10%/ < 10%	Present	Neg.	Segmental
14	IgAN(M1E0S1T0C0)	17/3	IgA 2–3 +,C3 1 +,IgM ±	±	< 5%/ < 5%	Present	Present	Major
15	ICMGN	53/0	IgA ±,C3 ±,IgM ± -1 +	Neg.	Neg./Neg.	Neg.	Neg.	Segmental
16	IgAN (M1E0S1T0C1)	23/4	IgA 3 +,C3 2 +,IgM– ±	Focal	< 5%/ < 5%	Neg.	Present	Major
17	MPGN	12/1	Neg.	Focal	Focal/Focal	Neg.	Neg.	Segmental
18	FSGS	20/1	IgM1 +	Focal	5%/Neg.	Present	Present	Segmental
19	DKD	15/10	Neg.	Multifocal	40%/Multifocal	present	Present	NA
20▲	IgAN(M1E0S1T0C1)	28/9	IgA3 +, IgM 1 +,C3 1 +	Focal	20%/Focal	Present	Present	Segmental
21	IgAN(M1E0S1T0C1)	19/3	IgA3 +, C3 ±	Focal	10%/Focal	Present	Neg.	Diffuse
22	MPGN	6/2	IgM1 +	Multifocal	35%/Multifocal	Present	Present	Segmental
23	DKD/CIN	15/1	IgG -, IgM +, IgA -, C3 -, C1q-	Focal	20%/Focal	Significant	Present	Segmental
24	AIN	33/0	IgM ±	Focal	Neg./Neg.	Present	Present	NA
25	AIN	17/0	IgG -, IgM ±, IgA -, C3 -, C1q-	Focal	Focal/Neg.	Mild	Neg.	Segmental
26	AIN	35/4	Neg.	±	Focal/Neg.	Neg.	Neg.	Segmental
27	AIN	30/0	IgA ±, IgM ±	Focal	Focal/Neg.	Neg.	Neg.	Segmental
28	AIN	20/2	IgM 1 +	Focal	Focal/Neg.	Present	Neg.	Segmental
29	CIN	13/5	IgM ±	Multifocal	70%/Multifocal	Significant	Present	Segmental
30※	CIN	13/2	IgM 1 +	Multifocal	40%/Multifocal	Present	Neg.	Major
31	AIN/ IgAN(M1E0S0T0C0)★	15/0	IgA 2 +,C3 ±	Multifocal	Neg./Neg.	Isolate	Neg.	Segmental
32◆	AIN	18/1	Neg.	Neg.	Neg./Neg.	Neg.	Neg.	Segmental
33	CIN	10/3	Neg.	Focal	35%/20%	Isolate	Present	Major
34	AIN	9/0	Neg	Extensive	10%/5%	Present	Neg.	Segmental

Table 2 (continued)

No	Pathology							
	Major diagnosis	Glom/sGlom	IF	ICI	TA/IFib	SAWT	SAH	PFPE
35	AIN	10/4	IgG ±	Moderate	< 5%/ < 5%	Significant	Present	Diffuse
36	AIN	20/4	Neg.	Extensive	5%/Neg.	Neg.	Neg.	Major
37	CIN	28/5	Neg.	Focal	< 3%/Neg.	Present	Present	Major
38	AIN	14/1	Neg.	Multifocal	< 5%/ < 5%	Neg.	Neg.	Segmental
39	AIN	45/1	Neg.	Focal	5%/Neg.	Neg.	Neg.	Neg.
40	CIN/DKD	13/4	Neg.	Multifocal	45%/Multifocal	Present	Present	Segmental
41※	AIN	11/0	Neg.	Multifocal	Neg./Neg.	Present	Neg.	Segmental
42	AIN/ IgAN(M0E0S0T0C0)★	15/2	IgA2 + ,IgM ±	Focal	5%/Focal	Neg.	Neg.	Segmental
43	SVD	17/7	Neg.	Multifocal	Multifocal/Focal	Significant	Present	Segmental
44	SVD	34/5	C3/C1q ±	Focal	Focal/Focal	Present	Present	Segmental
45	SVD	78/30	IgM ±	Multifocal	Focal/Focal	Significant	Present	Segmental
46	SVD	10/4	IgM ±	Focal	Focal/Focal	Significant	Present	Segmental
47▲	SVD	37/0	Neg.	Focal	Trace/Neg.	Significant	Present	Segmental
48	SVD	43/17	IgM ±	Focal	20%/Neg.	Significant	Present	Segmental
49	SVD	17/3	IgG ±	Focal	5%/5%	Significant	Present	NA
50	SVD	33/10	IgM ±	Focal	5%-10%/5%-10%	Present	Present	Major
51※	SVD	25/7	Neg.	Focal	< 3%/Neg.	Present	Neg.	Segmental
52※	SVD/DKD■	37/10	Neg.	Focal	20%/Focal	Present	Present	Segmental
53※	SVD	17/11	IgM1 +	Multifocal	40%/Multifocal	Present	Present	Neg.

GD, glomerular disease; TID, tubulointerstitial disease; SVD, small vascular disease; SCr, serum creatinine; AKI, acute kidney injury; 24hr-UPr, 24hr urinary protein; 24hr-UAE, 24hr urinary albumin excretion; HT, hypertension; DM, diabetes mellitus; Glom, number of glomerulus; sGlom, number of sclerosed glomerulus; IF, immunofluorescence; ICI, interstitial cellular infiltration; TA, tubular atrophy, IFib, interstitial fibrosis; SAWT, small arterial wall thickening; SAH, small arterial hyalinosis; PFPE, podocyte foot process effacement; GMC, minor glomerular change; IgAN, IgA nephropathy; DPGN, diffuse proliferative glomerular nephritis; CryoGN, cryoglobulinemic glomerular nephritis; DKD, diabetic kidney disease; MGUS, monoclonal gammopathy of undetermined significance; ICMGN, Immune complex mediated glomerulonephritis; ATN, acute tubular necrosis; AIN, acute interstitial nephritis; CIN, chronic interstitial nephritis; SVD, small vascular disease; Neg., negative; NA, not available.

★ AIN on top of IgAN, with AIN as the major cause of kidney dysfunction.

■ SVD on top of DKD,SVD is more evident to be the major cause of kidney dysfunction.

▲ the patient had microscopic hematuria.

● the patient was diagnosed MGUS.

◆ the patient had past history of gout, with prominent interstitial edema in the absence of glomerular change suggesting acute tubulointerstitial injury as the major cause of kidney dysfunction.

※ the patient had no 24hr-UPr, but urine PCR < 150 mg/g.

although the underlying mechanisms could possibly be more complex.

In the GD group, the majority of patients (15/23) had minor or non-severe pathological abnormalities (8 GMC, 7 IgAN, Table 2) that align with low-grade glomerular lesion corresponding to lesser urinary protein leakage. Similar scenarios had been reported in a number of glomerular diseases, such as in IgAN [10, 28–30] and DKD [7, 31, 32]. In 2015, Hoshino et al. reported that 35 out of 56 patients with isolated hematuria (mean eGFR 94.3 ± 18.3 ml/min per 1.73 m^2) had low-grade IgAN (gradeIor II of Lee's grading system) as the major pathological change [10]. Among T2DM patients with histologically confirmed DKD, the incidence of nonproteinuric or normal albuminuric diabetic nephropathy had been reported to be between 16.7 and 19.5% [7, 31]. Compared with their proteinuric counterparts, nonproteinuric DKD patients presented with following clinicopathological characteristics: (1) morphologically insignificant or low-grade glomerular lesion, (2) well-preserved interstitial and arteriolar compartments, (3) better blood pressure control, and (4) relatively well-preserved renal function [7, 24]. Nonetheless, it is noteworthy that a small fraction of DKD patients with significant structural and functional impairment in the kidney have normal albuminuria [7, 33, 34]. Such phenomenon was evident in the three DKD cases in our GD group (patient nos. 10, 19, 23 in

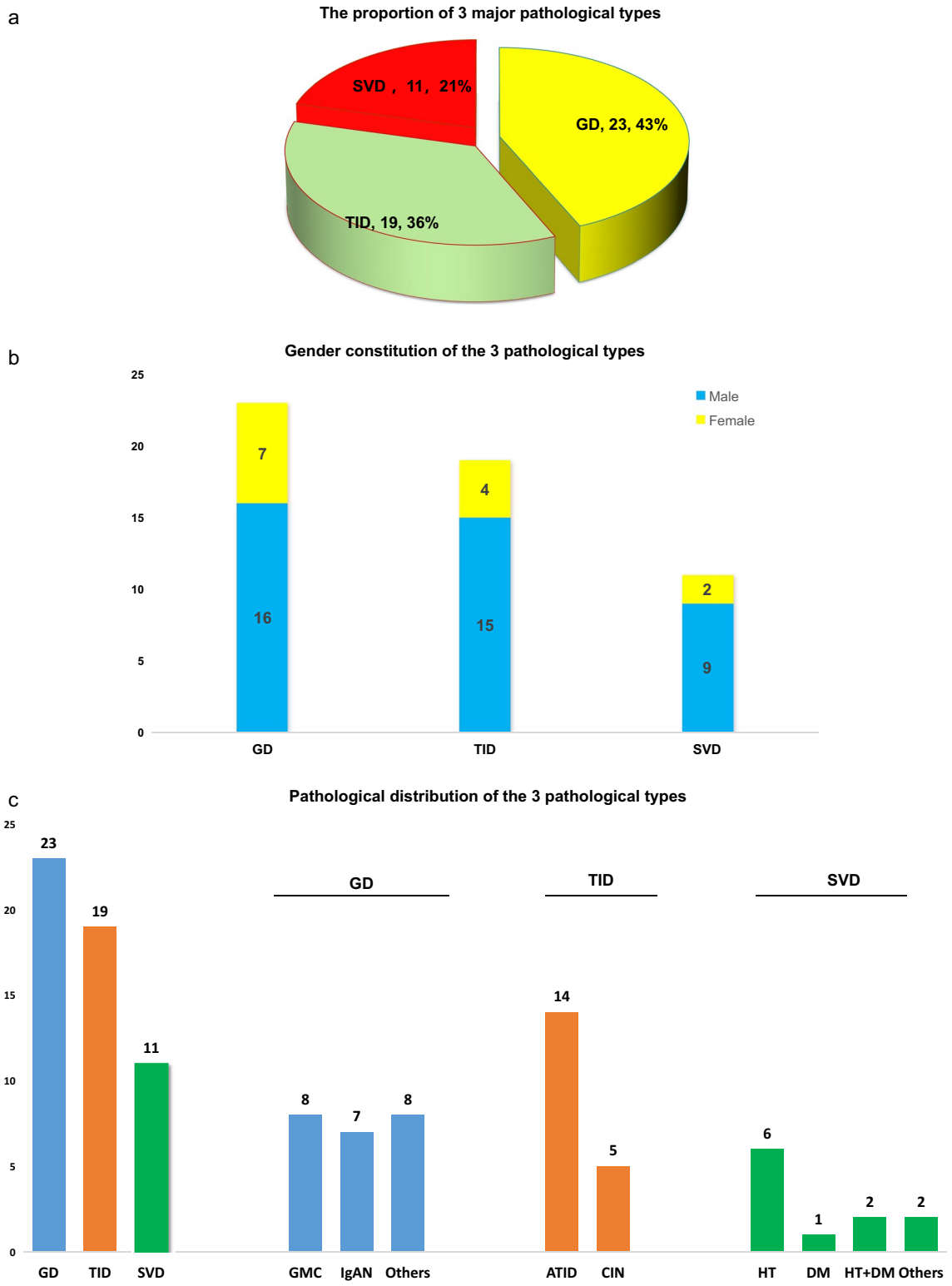

Fig. 2 The proportion, gender constitution and pathological distribution of 3 pathological types.

Table 2). They were two male and one female with a mean eGFR of 40.2 ml/min per 1.73m^2, and a history of DM and kidney dysfunction of about ten years. Their renal biopsies revealed sclerotic glomeruli and typical arteriolar sclerosis and hyalinosis, in the absence of K-W nodule (pathological features consistent with type III of Fioretto classification

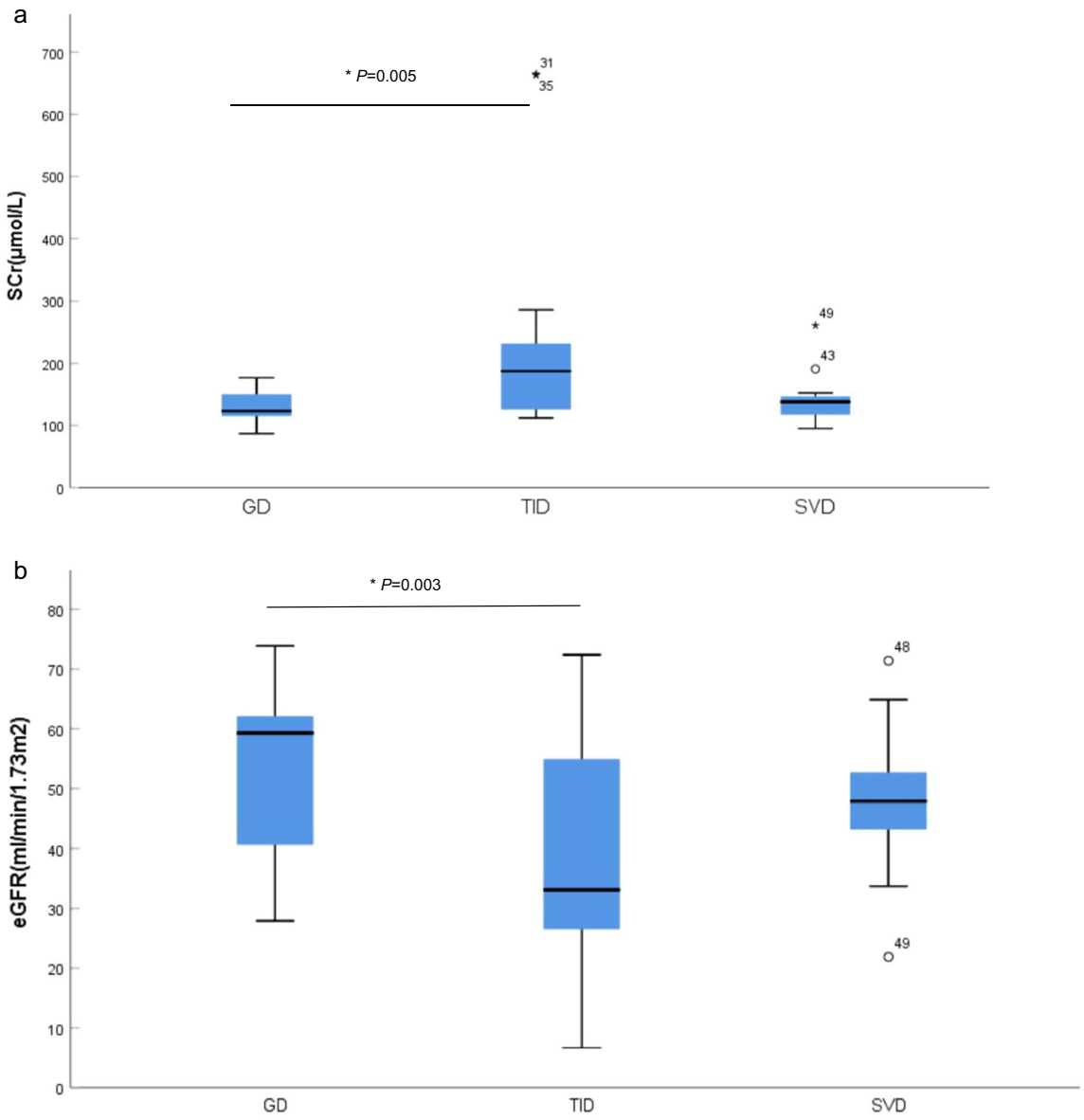

Fig. 3 **a** The mean SCr in the three pathological types, **b** The mean eGFR in the three pathological types.

Table 3 The mean eGFR and 24hr-UPr in the the three pathological types.

	Age(yr)	SCr(μmol/L)	eGFR(ml/min-1.73m^2)	24hr-UPr(mg)
GD	46.9 ± 13.3	129.7 ± 23.4	53.3 ± 13.4	100.7 ± 33.0
TID	46.1 ± 17.4	229.8 ± 161.7*	37.6 ± 18.7**	103.0 ± 27.3
SVD	50.4 ± 10.8	144.2 ± 46.4	47.9 ± 13.6	99.8 ± 21.0

GD, glomerular disease; TID, tubulointerstitial disease; SVD, small vascular disease

*significantly higher v.s. GD, $p = 0.005$

**significantly lower v.s. GD, $p = 0.003$

for diabetic nephropathy [35]), while their mean 24hr-UPr were only 87.2 mg. Comparable pathological-proteinuric dissociation had also been documented in, but not limited to, lupus nephritis [36, 37] and obesity-related glomerulopathy [26]. In our study, a 68-year-old female patient was found to have cryoglobulinemic DPGN. She presented with AKI and her eGFR was 27.9 ml/min per 1.73 m^2 at the time of renal biopsy, while the 24hr-urinary protein/albumin was only 113.7 mg/50.2 mg, with no microscopic hematuria. Her renal function significantly improved after treatment with pulse steroid, plasma exchange and rituximab.

Acute interstitial nephritis (AIN) reportedly accounted for 15–27% of renal biopsy findings among subjects of acute kidney injury, for which the causes might involve

drug, infection, systemic disease and idiopathic origin [38]. The urinary protein excretion in acute tubulointerstitial diseases is typically modest with median or mean values of 0.7 g (0.39, 1.0)/24hr [39] or 0.9 ± 1.1 g/24hr (range, 0–6 g) [40] in different cohorts. The reported incidence of non-proteinuric AIN was infrequent, ranging between 4.5 [38] and 8% [40], which could be owing to preserved protein resorption function of renal tubules. In our series, ten of the patients presented with AKI, of whom nine (90%) exhibited tubulointerstitial disease; eight out of these nine cases had a history of diarrhea prior to biopsy, implying acute gastroenteritis as the trigger of AKI. In the TID group, a higher incidence of AKI and more extensive tubulointerstitial involvement might account for its lowest eGFR amongst the three groups (Table 2).

The fraction of HT (8/11) in the SVD group is the highest among the three groups. Six of the 11 cases had isolate HT (without DM) and 1 patient with isolate DM (without HT); arteriolar hyalinosis and significant small vascular wall thickening were observed in these seven patients. Whereas, four patients in the GD group with intercurrent HT and DM registered no apparent small vascular change (patient nos. 1, 6, 10, 13, Table 2), which is thought to be related with younger age, shorter disease vintage, or possibly, limited specimen tissue. The resistant blood vessels (small artery and arterioles, with lumen diameters in-between 15 and 300 μm) are early targets of HT and DM. Endothelial cell is now recognized as the primary site of tissue injury in both conditions. HT and DM, via multiple pathways, induce endothelial dysfunction and subsequent vasospasm and mural remodeling of small vessels [41, 42]. Both HT and DM are known to cause arterial wall thickening and luminal narrowing. Another feature of hypertensive and diabetic vascular disease is small artery hyalinosis, which is associated impaired vascular autoregulation and is a marker of reduced blood flow and hypoxemia of renal interstitium [43]. Similar histological changes can also be seen in the elderly due to vascular ageing. The typical pathological abnormalities of hypertensive nephrosclerosis (HTN) include glomerular ischemia (induced by afferent arteriolar sclerosis) and glomerular hypertrophy and sclerosis (secondary to hyperperfusion). Whereas DM may induce pathological damage in every compartment of the kidney, the most characteristic of which is (K-W) nodular glomerular sclerosis that results from excessive extracellular matrix accumulation and mesangial expansion. But the degree of the renal damage depends as well on the disease severity, duration, and the genetic predisposition of individual HT and DM patient [44–46]. It is notable that either small arterial sclerosis or hyalinosis is not pathognomic in HTN or DKD [47]. Renal vascular lesions are observable in a variety of nephropathies that are independent of systemic hypertension [48]. This phenomenon is thought to be attributable to the activation of RAAS (renin angiotensin and aldosterone system) of local tissue [47]. As shown in our series, six cases (26.1%, patient nos. 7, 11, 14, 18, 20 and 21) of the GD group and seven cases (35%, patient nos. 28–31, 37, 40, 43) in the TID group had no background HT or DM, but arteriolar hyalinosis and/or small vascular wall thickening of variable degree were identified (Table 2).

Podocyte foot process and slit diaphragm are the key components to maintain glomerular basement membrane (GBM) selectivity. 46 of the 50 patients with available EM data invariably showed different degrees of PFPE (segmental in 31 [67.4%], major in 12 [26.1%], and extensive effacement in three [6.5%], Table 2). PFPE results from fusion and flattening deformation of foot process, due to the disruption and reorganization of its actin cytoskeleton. It is an energy-consuming adaptive response of podocyte to trade off excessive damage under various pathological stressors [49, 50]. PFPE is potentially reversible if stressful insult is resolved [50]. The relative moderate PFPE change observed in our series is a reflection of nonsevere podocyte injuries in general.

Admittedly there were limitations in this study that include pathological methodology, retrospective nature and a relative small patient number. The classification of our patients are mainly based upon morphological study in conjunction with clinical data and judgements of the reviewers, which may potentially compromise accuracy. Since molecular pathology, given available, is more informative and specific, capable of differentiating overlapping zone or even disproving the diagnosis made by a routine approach [51]. Some other factors, such as PRB indication adopted, clinician's input, geography, disease epidemiology and patient consent, among others, may swing patient selection and study outcome [52]. The difference in the rate of enrollment of the three centers provided some thought in this connection. It is our hope that this study may serve to provide experience, reference and insight to assist clinical decision-making.

Conclusions

In summary, we conducted a retrospective investigation of the renal histopathology in patients presenting with non-proteinuric kidney dysfunction, a situation by no means rarely encountered in practice. Analyses indicated GD, followed by TID, accounted for around 80% of 53 cases enrolled; SVD was the pathological subtype in the rest of 20% patients. Renal dysfunction of normal-range proteinuria may possibly, but not necessarily, be related with histologically nonsevere glomerular disease, or tubular-interstitial involvement. In a patient with a history of hypertension, small arterial or

arteriolar sclerosis could be considered as the underlying cause of his/her kidney dysfunction.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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