Original paper

Clinicopathologic analysis of isolated hematuria in child/adolescent and adult patients

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To our knowledge, no in-depth clinicopathologic study of isolated hematuria (IH) is currently available. To address this gap, we analyzed the clinicopathologic features of IH as it manifests in child/adolescent and adult patients. The clinical data and pathological types of 543 IH patients who underwent renal pathological examinations from January 2005 to June 2010 were retrospectively analyzed. Clinical manifestations differed among the age groups: children/adolescents exhibited the highest percentage of mesangial proliferative glomerulonephritis (41.78%), whereas adults showed the highest percentage of immunoglobulin A nephropathy (IgAN) (52.39%). In addition, the percentage of IH patients who were classified according to clinical pathology differed from that of patients who were classified according to renal pathological type. Patients with IgAN who were found to have minimal proteinuria had more severe IH. For IH patients, especially those with a small amount of proteinuria, renal biopsy should be performed as early as possible in order to develop a long-term treatment plan and prognosis evaluation.

Key words: isolated hematuria, clinical, pathology, child, adolescent, adult.

Introduction

Isolated hematuria (IH) refers to renal disease that is clearly diagnosed as glomerular hematuria. IH patients exhibit elevated red blood cell (RBC) counts and no other clinical symptoms or changes during renal function tests [1, 2, 3]. IH can manifest as paroxysmal gross hematuria or persistent microscopic hematuria, which is not accompanied by edema, hypertension, or renal insufficiency [4, 5]. The etiology and pathogenesis of these two forms of IH, as well as their treatment and prognosis, are very different [4, 5].

With the improvement in general wellness and the popularity of urine tests, the number of IH patients has also increased. An epidemiological survey of 6,311 urban cases (patients > 20 years old) in Guangzhou, China, showed that hematuria has an incidence rate of 3.8% (95% confidence interval [CI]: 3.4%, 4.3%) [6]. Vivante *et al.* [7] performed a 22-year follow-up assessment of cases of isolated microscopic hematuria among 3,690 Israeli adolescents and discovered that 0.7% of patients progressed to end stage renal disease (ESRD). Only 0.045% of non-microscopic hematuria patients also progressed to ESRD, so persistent asymptomatic microscopic hematuria in adolescent populations was considered an independent risk factor for ESRD. Thus, prompt treatment should be a cornerstone of the treatment approach in the wake of an IH diagnosis. However,

very few studies have focused on IH. In fact, no in-depth study of IH clinicopathologic features has been conducted to date.

In this article, clinically diagnosed IH patients underwent renal biopsy examination to further reveal the characteristics and course of IH. The clinicopathologic features in children and adult patients were then compared and analyzed.

Material and methods

A total of 543 patients were diagnosed with IH and underwent renal pathological examinations from January 2005 to June 2010 in our hospital. The patients were aged between 1.1 years old and 77 years old (mean age 29.72 ±15.91 years old). The patients included 277 males and 266 females, with a male-to-female ratio of 1.04 : 1. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Beidaihe Sanatorium of Beijing Military Area Command. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

The counting of centrifuged urinary RBCs > 3/HP and/or urinary sediment RBC > 8×10^3/ml was set as the diagnostic criteria for hematuria. The inclusion criteria were as follows: 1) urinary test results had to meet the above diagnostic criteria two or more times, and 2) urinary samples had to exhibit severely deformed RBC (e.g., ring-like appearance, presence of spores or perforation) ≥ 30% or multiple malformed RBC ≥ 75%. Exclusion criteria were as follows: 1) 24-hour urinary protein ≥ 0.3 g; 2) serum creatinine ≥ 132.6 μmol/l; 3) edema; 4) abnormal blood pressure; 5) immunological abnormalities, including blood anti-O chain, complementary C3, HBsAg, HCVAb, or autologous antibodies; 6) secondary renal diseases, including diabetic nephropathy, lupus nephritis, or purpura nephritis; 7) diseases exhibited in the family history such as Alport syndrome; or 8) urinary calculus, urinary tuberculosis, hypercalciuria, urinary tract malformation, urinary tract cancer, left renal vein entrapment syndrome-induced hematuria, or other physiological urinary abnormalities. Indications of renal biopsy were as follows: 1) history of microscopic hematuria ≥ 6 months and gross hematuria sustained more than half a month or reoccurring twice, and 2) the cause could not be confirmed by a conservative screening method.

Clinical test methods

Blood pressure measurements and physical examinations were performed routinely. Laboratory tests included a routine urine examination, urinary sediment analysis, quantitation of 24-h urinary protein, urine three-cup test with urinary RBC morphology, serum C3, C4, CH50, anti-O chain evaluation, serum protein electrophoresis, blood urea nitrogen (BUN), urinary tract ultrasound, and analysis of serum creatinine, serum electrolytes, autologous antibodies, and serum markers of hepatitis B and C. The microscopic examination of urinary RBCs was performed as follows: the middle segment of fresh morning urine was obtained and then mixed and placed in a 10-ml centrifuge tube for centrifugation at 1,500 rev/min for 5 min. The sediment was approximately 0.5 ml. The amounts of urinary RBCs and abnormal RBCs in 1 ml of urine were determined to calculate the percentage of abnormal RBCs. Each patient was made to undergo urinary RBC examination at least twice, and two examiners evaluated each specimen at least twice. A urinary sediment RBC count was performed toward the middle segment of the fresh morning urine with a UF-100i Automated Urine Particle Analyzer (Sysmex Corporation, Kobe, Japan).

Pathological examination

Methods included light microscopy and immunofluorescence, and certain individual cases underwent electron microscopic examination. The specimens for light microscopy included 10 or more renal glomeruli that underwent paraffin embedding. The slice thickness was ≤ 3 μm, and hematoxylin and eosin (HE), periodic acid-Schif (PAS), periodic Schiff-methenamine (PASM) and Masson's staining were performed. Patients with kidney damage caused by suspected ingredients underwent special staining (i.e., Congo red staining); the frozen sections were used for immunofluorescence. Fluorescein isothiocyanate-labeled, goat anti-human IgG, IgA, IgM, C3, C4, C1q, and Fib were used for direct immunofluorescence. Finally, the biopsy specimens of individual cases based on the requirements of the clinical diagnosis were sent for transmission electron microscopic examination at the Center of Electron Microscopy at the Third Hospital of Peking University. Observations included the thickness and structure of glomerular basement membrane, electron-dense materials and their deposition sites, morphology and cell inclusion of foot processes of glomerular epithelial cells, and anomalous fiber-like substances and virus-like particles.

Pathological diagnosis

According to the World Health Organization's classification of glomerular disease (1995) [8], pathological diagnosis should be divided into glomerular mild lesions (GML), mesangial proliferative glomerulonephritis (MsPGN), and endocapillary proliferative glomerulonephritis (EnPGN). In our study, GML ex-

hibited no obvious lesions under a light microscope, or only mild mesangial hypercellularity, and negative or weakly positive immunofluorescence; electron microscopy showed no characteristic lesions. MsPGN light microscopy revealed that the mesangial cells and matrix exhibited mild, moderate, or severe diffuse hyperplasia, while immunofluorescence revealed IgG and complement C3 depositions in different mesangial areas with different intensities. These depositions were sometimes associated with the inner portion of the basal membrane; electron microscopy revealed mesangial proliferation associated with the deposition of low-density electron-dense materials. EnPGN light microscopy revealed diffuse proliferation of endothelial cells and mesangial cells, and immunofluorescence revealed IgG deposition and complementary C3, as coarse granules, along the outer side of the basal membrane; these were sometimes associated with depositions in the mesangial area. Electron microscopy revealed the proliferation of endothelial cells and mesangial cells, as well as camel hump-like, electron-dense deposits outside of the basal membrane; electron-dense material deposits could be seen in the mesangial areas (Fig. 1).

Among the three types of glomerular disease, the pathological changes of IgAN were analyzed and divided into classes I to V based on Lee's grading standards (Table I) [9]. The diagnostic criteria for MsPGN referred to in the literature were divided into mild (i.e., the proliferating mesangial cells and/or mesangial matrix did not exceed the capillary diameter), moderate (i.e., the proliferating mesangial cells and/or mesangial matrix exceeded the capillary diameter, and the capillary lumen was squeezed) or severe (i.e., the proliferating mesangial cells and matrix had destroyed the capillary loops, initiating a segmental sclerosis state). In addition, several cases of thin basal membrane nephropathy and membranoproliferative nephritis were noted; these cases were rare, and thus were included with other classifications.

Grouping

Age groupings included: 1) child/adolescent (< 18 years old when treated): 146 cases, or 2) adult (aged ≥ 18 years old when treated): 397 cases. **Clin-**

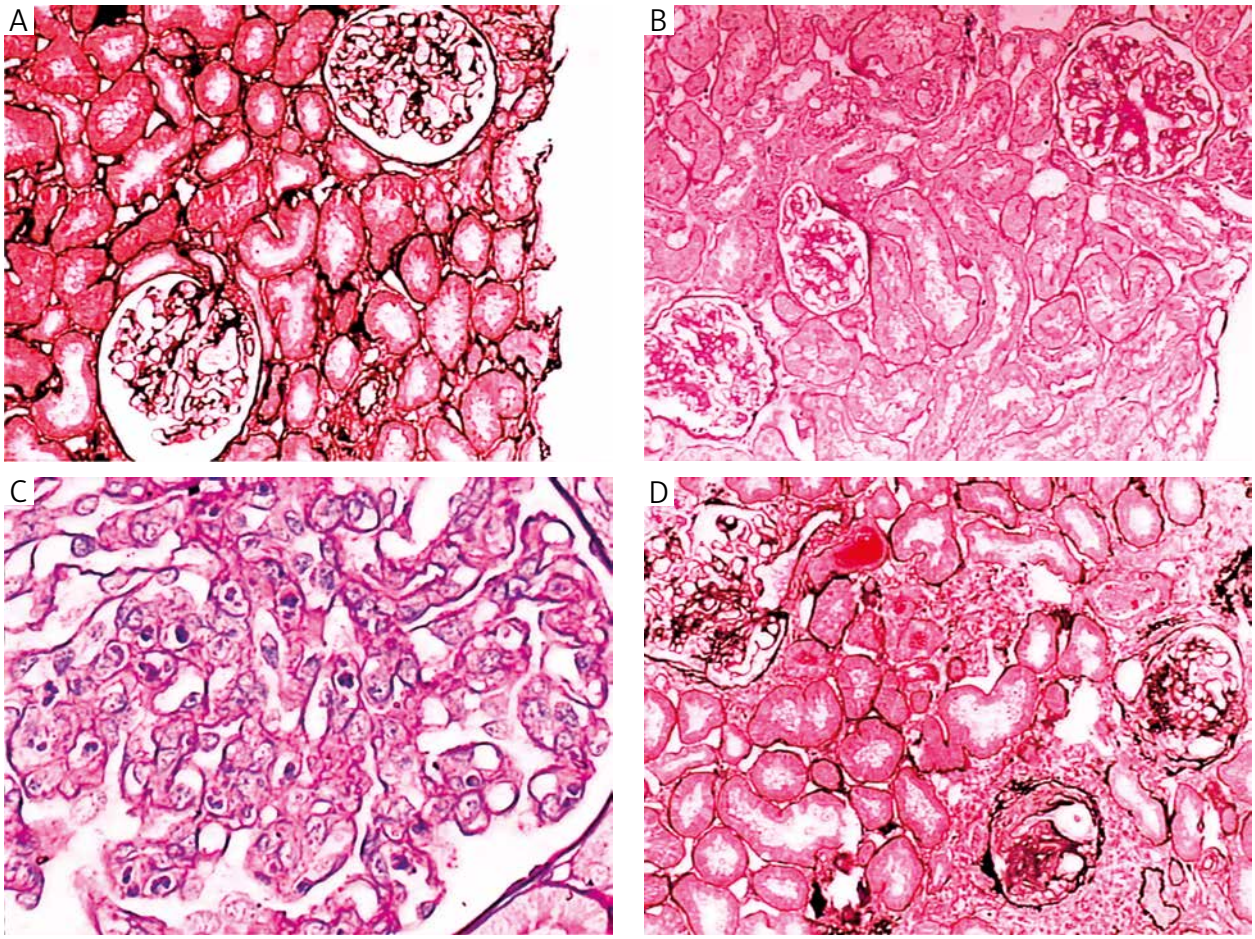

Fig. 1. Pathological figures and explanation of IgAN. A) mild lesions in renal glomerulus (PASM, 100×); B) mesangial proliferative glomerulonephritis (PAS, 100×); C) endocapillary proliferative glomerulonephritis (PAS, 400×); D) local proliferative sclerotic IgA nephrosis (level Lee IV) (PASM, 100×)

Table I. Lee 's classification of IgAN

Classification	Renal glomerulus	Renal tubule	Renal interstitium
I	Normal	No lesion	No lesion
II	Less than half of glomerular mesangial cells and matrix exhibited mild hyperplasia or focal segmental sclerosis	No lesion	No lesion
III	Mesangial cells and matrix exhibited diffuse mild to moderate hyperplasia, the focal segmental sclerosis increased, and balloon adhesions and small crescents could be occasionally seen	Focal renal tubular atrophy	Edema in focal renal interstitium and inflammatory cell infiltration could be seen
IV	Mesangial cells and matrix exhibited diffuse moderate and severe hyperplasia, 45% or less of glomerular cells exhibited crescents and hardening	Multifocal tubular atrophy	Multifocal inflammatory cell infiltration in renal interstitium
V	Similar to class IV, while much more severe, or more than 45% of glomerular cells exhibited crescents	Similar to class IV, but much more severe	Similar to class IV, but much more severe

ical groupings included: 1) microscopic and gross hematuria (MGH): 171 cases exhibiting microscopic hematuria and/or gross hematuria (quantitation of 24-h urinary protein was < 0.15 g), or 2) small amount of proteinuria (SAP): 372 cases (quantitation of 24-h urinary protein, 0.15-0.3 g) with accompanying microscopic hematuria and/or gross hematuria. **Pathological grouping** was based on the type of pathological diagnosis and Lee's IgAN classification.

Statistical analysis

All statistical processes were performed with SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Measurement data are represented as $\bar{x} \pm s$, with the non-parametric data represented by the median and the counting data expressed as the percentage. The intergroup comparisons of the measurement data were determined with t or rank sum tests, whereas the intergroup comparison of the counting data was determined by the χ^2 test. Pearson test, the Yates correction method, or Fisher's exact test was selected according to the specific data, with $P < 0.05$ considered as statistically significant.

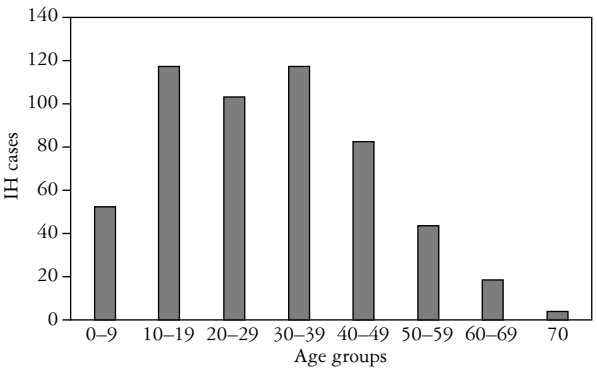

Fig. 2. IH cases of different age groups

Results

Clinical manifestations

The IH percentage was calculated according to the age groupings. The percentage of 10- to 39-year-old patients was higher, accounting for 62.61% of the sample size (Fig. 2), and there was a higher percentage of male patients when the child/adolescent and adult groups were compared. The medians of disease duration for the two groups (i.e., from onset to renal biopsy) were clearly different at 2.5 months (0.4 months to 79.5 months) and 7.1 months (0.5 months to 251.4 months), respectively. The hematuria percentage among children/adolescents being treated for respiratory tract infections was higher than that of the adult group, whereas more adults were diagnosed with IH when they had lumbar symptoms and during the course of their normal physical exanimations. No difference in the incidence rate of gross hematuria was found between the age groups, but the adult group exhibited a higher proportion of SAP than the children/adolescents (Table II).

Pathological characteristics

The renal pathological type of the child/adolescent group differed from that of the adult group, with the children/adolescents having the highest percentage of MsPGN. The pathological types of GML, MsPGN, and EnPGN were much more common in the child/adolescent group, whereas the IgAN percentage was the highest and more common in the adult group (Table III).

Clinical aspects and pathology

Differences were observed in the renal pathological constituent percentage among the different clinical groupings of IH patients. For example, the MsPGN

Table II. Clinical manifestations of IH in different age groups

Clinical manifestations	Child/adolescent (%)	Adult (%)	χ^2	P
Cases	146	397	–	–
Age at diagnosis (years)	10.78 ±3.74	36.69 ±12.66	–	–
Gender ratio (M : F)	88 : 58 = 1.52 : 1	189 : 208 = 0.91 : 1	6.854	0.009
Duration (months)	2.5 (0.4~79.5)	7.1 (0.5~251.4)	–	0.000
Causes of discovery				
Respiratory infection	23 (15.75%)	30 (7.56%)	8.142	0.004
Urinary tract infection	2 (1.37%)	11 (2.77%)	0.397	0.529
Lower back discomfort	1 (0.68%)	36 (9.07%)	11.814	0.001
Normal physical examination	12 (8.22%)	81 (20.40%)	11.164	0.001
Gross hematuria	17 (11.64%)	39 (9.82%)	0.382	0.536
Accompanied by SAP	89 (60.96%)	283 (71.28%)	5.275	0.022

Table III. Pathological features of different age groups of IH patients

Grouping	n	GML	MsPGN	IgAN	EnPGN	Others	χ^2	P
Child/adolescent (%)	146	15 (10.27)	61 (41.78)	48 (32.88)	16 (10.96)	6 (4.11)	35.665	0.000
Adult (%)	397	19 (4.79)	149 (37.53)	208 (52.39)	7 (1.76)	14 (3.53)		

GML – glomerular mild lesions; MsPGN – mesangial proliferative glomerulonephritis; IgAN – IgA nephropathy; EnPGN – endocapillary proliferative glomerulonephritis

Table IV. Clinicopathologic features of IH patients

Grouping	n	GML	MsPGN	IgAN	EnPGN	Others	χ^2	P
MGH group (%)	171	12 (7.02)	84 (49.12)	64 (37.43)	7 (4.09)	4 (2.34)	13.511	0.009
SAP group (%)	372	22 (5.91)	126 (33.88)	192 (51.61)	16 (4.30)	16 (4.30)		

MGH – microscopic and gross hematuria; SAP – a small amount of proteinuria; GML – glomerular mild lesions; MsPGN – mesangial proliferative glomerulonephritis; IgAN – IgA nephropathy; EnPGN – endocapillary proliferative glomerulonephritis nephritis

Table V. Clinicopathologic characteristics of different age groups of IH patients

Age group	Grouping	n	GML	MsPGN	IgAN	EnPGN	Others	χ^2	P
Child/adolescent	MGH (%)	57	4 (7.02)	32 (56.14)	15 (26.32)	5 (8.77)	1 (1.75)	8.474	0.076
	SAP (%)	89	11 (12.36)	29 (32.58)	33 (37.08)	11 (12.36)	5 (5.62)		
Adult	MGH (%)	114	8 (7.02)	52 (45.61)	49 (42.98)	2 (1.76)	3 (2.63)	7.514	0.111
	SAP (%)	283	11 (3.89)	97 (34.28)	159 (56.17)	5 (1.77)	11 (3.89)		

MGH – microscopic and gross hematuria; SAP – a small amount of proteinuria; GML – glomerular mild lesions; MsPGN – mesangial proliferative glomerulonephritis; IgAN – IgA nephropathy; EnPGN – endocapillary proliferative glomerulonephritis nephritis

Table VI. Clinicopathologic features of MsPGN in children/adolescents and adults

Age group	Clinical grouping	n	Mild MsPGN	Moderate MsPGN	Severe MsPGN	χ^2	P
Child/adolescent	MGH (%)	32	32 (100.00)	0 (0.00)	0 (0.00)	4.724	0.094
	SAP (%)	29	25 (86.21)	3 (10.34)	1 (3.45)		
Adult	MGH (%)	52	45 (86.54)	6 (11.54)	1 (1.92)	4.289	0.117
	SAP (%)	97	71 (73.20)	17 (17.53)	9 (9.27)		

MGH – microscopic and gross hematuria; SAP – a small amount of proteinuria; MsPGN – mesangial proliferative glomerulonephritis

Table VII. Clinicopathologic features of IgAN in children/adolescents and adults

Age group	Clinical grouping	n	Grade I IgAN	Grade II IgAN	Grade III IgAN	Grade IV IgAN	Grade V IgAN	χ^2	P
Child/adolescent	MGH (%)	15	0 (0.00)	14 (93.33)	1 (6.67)	0 (0.00)	0 (0.00)	2.771	0.428
	SAP (%)	33	1 (3.03)	24 (72.73)	7 (21.21)	1 (3.03)	0 (0.00)		
Adult	MGH (%)	49	2 (4.08)	30 (61.22)	12 (24.49)	5 (10.21)	0 (0.00)	17.650	0.001
	SAP (%)	159	1 (0.63)	52 (32.70)	75 (47.17)	28 (17.61)	3 (1.89)		

Note: MGH: microscopic and gross hematuria, SAP: a small amount of proteinuria, IgAN: IgA nephropathy

percentage in the MGH group was higher than that of the SAP group, whereas the IgAN percentage in the former was lower than that in the latter (Table IV). Regardless of age of the IH patients, no difference was observed in the renal pathological constituent percentage among the MGH groups when the patients were grouped according to different clinical manifestations (Table V).

In terms of the pathological changes in MsPGN and IgAN, cases of mild MsPGN exhibited the highest percentage of changes. No differences were generally found in the extent of MsPGN lesions among the different clinical groups (Table VI). Lee grade II had the highest percentage among the different clinical groups of IgAN in children/adolescents, whereas no difference was generally observed in Lee's classification among the different clinical groups. For the cases of adult IgAN, the highest Lee grade II was found in the MGH group and the highest Lee grade III was found in the SAP group. A comparison between the two groups showed that Lee grades I and II in the MGH group were higher than those in the SAP group, whereas Lee grades III and IV in the MGH group were lower than those in the SAP group (Table VII).

Discussion

Our study showed that 10- to 39-year-old patients accounted for 62.61% of the total cases of IH. The percentage of patients older than 40 years old was remarkably decreased, which might be related to age-related changes in the renal-specific disease spectrum and other factors. However, the lack of epidemiological investigation results did not directly reflect the incidence within this age range. When grouped by age, the child/adolescent group had a higher percentage of males than the adult group, probably because the IgAN percentage in male IH children was higher than in females [10]. The duration medians of the two groups (i.e., from onset to renal biopsy) were clearly different at 2.5 months (0.4 months to 79.5 months) and 7.1 months (0.5 months to 251.4 months), respectively, because the children/adolescents tended to visit the hospital earlier and a higher degree of attention was paid to their symptoms. The hematuria percentage among children/adolescents hospitalized for respiratory infection was higher than that of adults, whereas more adults were diagnosed when they went to the hospital for lumbar symptoms and normal physical examinations. These results indicate the need for vigilance regarding clinical manifestations of IH and prodromal symptoms in different age groups. Medical examinations are especially important for adults who receive an early IH diagnosis. No difference in the incidence of gross hematuria was found between the different age groups, whereas the SAO percentage in the adult group was higher than that in the child/adolescent group. Through further clinical and pathological analyses, we revealed the pathological basis of this clinical feature.

The pathological appearances of IH are diverse. Zhang and Shen [11] reported that thin basement membrane nephropathy (TBMN), IgAN, MsPGN are the three most common renal pathologies in children diagnosed with IH. Elsewhere, Mo and Chen [12] reported that the renal pathological result order was most commonly MsPGN, ML, and IgAN. A recent study [5] showed that GML accounts for most pathological types of IH in children, followed by IgAN, TBMN, and MsPGN. Hall *et al.* [13] reported the biopsy results of 89 adult cases of asymptomatic microscopic hematuria; TBMN, IgAN, GML, and normal kidney tissue accounted for 43%, 20%, 19%, and 18% of cases, respectively, which is similar to the percentages seen for the pathological constituents of children's IH.

Our study shows that pathological types differ among age groups. MsPGN was the most common in the child/adolescent group, followed by IgAN, EnPGN, and GML. By contrast, IgAN accounted for more than 50% of IH patients in the adult group, followed by MsPGN, GML, and EnPGN. Although reports varied by pathological type, the above data show that most IH patients exhibited mild renal pathology, whereas a small percentage had more severe pathological lesions. Experts should thus be cautious, especially when evaluating adult IH patients, who exhibit a higher IgAN percentage. Renal biopsy should be actively conducted to confirm the pathological type and thus initiate the most effective therapy. As for

child/adolescent IH patients, although MsPGN accounted for the highest percentage of cases, IgAN still accounted for more than one quarter (26.32%) of cases; hence the prognosis for IH patients is not benign [14, 15, 16]. Renal biopsy should also be considered to achieve early diagnosis and appropriate treatment.

Studies of the relationship between clinical and pathological factors of IH patients have shown that MsPGN and IgAN are the two most common pathological types among different clinical manifestations. These two types accounted for more than 85% of cases, where the MGH group was associated with the highest percentage of MsPGN (49.12%), followed by IgAN, GML, and EnPGN. In the SAP group, IgAN accounted for the highest percentage (52.61%) of cases, followed by MsPGN, GML, and EnPGN. These results differed from previous studies [3, 5, 17, 18, 19, 20] and might be related to differences in the inclusion and exclusion criteria of the various studies, especially proteinuria standards. For example, in the study of Parmar [21], a urinary protein excretion rate < 1 g/d was the inclusion criterion, whereas Chow *et al.* [17] set the proteinuria level at 0.3 ± 0.1 g/d. Given that a higher baseline protein excretion rate was selected by Chow and colleagues, the pathological types were more severe than in Parmar's study. In the present study, the patients were grouped according to age. Regardless of the age of the patients, no difference was found in the constituent percentage of pathological types among the different clinical groups. Further analysis of patients with MsPGN revealed that different age groups exhibiting dissimilar clinical manifestations had mild MsPGN. The analysis of patients with IgAN showed that among children/adolescents, Lee grade II IgAN was the most common among IH patients with different clinical manifestations. In the adult group, the MGH group most commonly exhibited Lee grade II IgAN. The SAP group most commonly exhibited Lee grade III IgAN, and pathological classifications were generally more severe than in the MGH group. Microalbuminuria was a sensitive indicator of early renal injury [22]. Our study shows that the detection of microalbuminuria level in IH patients, especially in adult patients, has some clinical significance in determining pathological type.

In summary, IH patients of different age groups exhibited different clinical manifestations and pathological features. The IH patients with different clinical manifestations also had diverse pathological types: the percentage of cases of IgAN, which can lead to progressive renal injury, was relatively high, especially in adult IH patients and SAP-accompanied patients. When IgAN patients exhibited SAP, the severity of the disease was much more serious. Although major nephrology physicians still believe that IH follows a relatively benign course and biopsy does not affect treatment options or prognosis, our study again illustrates the importance and necessity of early renal biopsy for clinically diagnosed IH. Renal biopsy, which is particularly important for those who have SAP, can help physicians develop a long-term treatment plan and prognosis evaluation.

The authors declare no conflict of interest.

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