Research Article

Feng Liu, Chenyu Wang, Rongzhen Wang, Wenge Wang, Min Li*

Henoch-schonlein purpura nephritis with renal interstitial lesions

https://doi.org/10.1515/med-2018-0088
received July 26, 2017; accepted October 26, 2018

Abstract: Objective: To investigate the clinical pathology and prognosis & outcome of Henoch-Schonlein purpura nephritis (HSPN) with renal interstitial lesions.

Methods: All 148 patients were analyzed for clinical, renal pathological, and prognostic features. Patients with no, mild, and moderate- severe renal tubulo-interstitial lesions were included in group A, B and C, respectively.

Results: The estimated glomerular filtration rate (eGFR) of group B was significantly lower than that of group A. The levels of serum creatinine and blood urea nitrogen in group C were significantly higher than those in groups A and B. Clinical type II was correlated with pathological types II and IIIa; pathological type IV and IIIb were correlated with clinical type VI and IV. There were significant differences in the level of red blood cells in urinary sediment, levels of urine occult blood and in the prognosis among the 3 groups.

Conclusion: Clinically, Type II is the most common cause; pathologically, Type IIIa is more common. The severity of renal tubulo-interstitial lesions is positively correlated with a decline in renal function and GFR. There is a correlation between the severity of renal tubulo-interstitial lesions and the severity of hematuria. Most patients with HSPN have a good prognosis.

Keywords: Renal interstitial lesions; Clinical manifestations; Pathological manifestations

***Corresponding author: Min Li,** Institute of Pathology, Basic Medical College of Lanzhou University, Lanzhou 730000, Gansu Province, China. Tel: +86-0931-8915021, Fax: +86-0931-8915021, E-mail: limin1779@163.com
Feng Liu, Chenyu Wang, Institute of Pathology, Basic Medical College of Lanzhou University, Lanzhou, Gansu Province, China
Rongzhen Wang, Department of Nephropathy, The First Hospital of Lanzhou University, Lanzhou, Gansu Province, China
Wenge Wang, Department of Nephropathy, Lanzhou University Second Hospital, Lanzhou, Gansu Province, China

Abbreviations: Henoch-Schonlein purpura (HSP); Henoch-Schonlein purpura nephritis (HSPN); urine protein (UTP); N-acetyl β-D-glycosaminidase (NAG); Periodic Acid-silver Methenamine (PASM)

1 Introduction

Henoch-Schonlein purpura (HSP) is a systemic vasculitis featured by pathological changes such as small vasculitis . Symptoms of multi-organ injury may occur in these patients [1]. The incidence of this disease is between 30% and 60%. HSP accompanied with renal injury is called Henoch-Schonlein purpura nephritis (HSPN) [2]. About 20% of patients with HSPN can develop nephritic syndrome and nephrotic syndrome [3]. The progression of this disease to chronic renal injury and end-stage renal failure is rare for it is a self-limited disease [3]. This disease is more common in children, and ranked first in secondary kidney diseases in children, and second in secondary nephritis in adults [4]. In a study of HSP in Asian adults, 56% of them were found to have renal injury [5]. It is now recognized that a large number of proteinuria, early renal insufficiency, severe glomerulosclerosis and extensive crescent formation are important factors for poor prognosis of HSPN [6]. It has also been reported that renal tubular lesions and renal interstitial fibrosis also affect the prognosis of HSPN [7]. This study explored the correlation between renal interstitial lesions and clinical pathology based on the pathogenetic characteristics of this disease and from the perspectives of pathology, clinical manifestations and prognosis & outcome of patients with HSPN.

2 Materials and methods

A total of 148 patients diagnosed as purpura nephritis at The First Hospital of Lanzhou University and Lanzhou University Second Hospital from September 2007 to June 2012 were collected. All cases met the diagnostic criteria of HSPN [8], and the number of glomeruli observed by the

microscope on renal biopsy was not less than 10. Patients with IgA nephropathy and other secondary diseases such as systemic lupus erythematosus and Anti-Neutrophil Cytoplasmic Autoantibodies-associated nephritis were excluded. This study was approved by the Ethics Committee of The First Hospital of Lanzhou University and followed the guidelines of Helsinki Declaration. Informed consents were obtained from all the subjects.

A retrospective case-control study was conducted to analyze the clinical and pathological data of patients (e.g., age, gender, onset season, clinical symptoms, severity of hematuria, severity of proteinuria, blood biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 24-hour urine protein (UTP), urinary β2 microglobulin, urinary N-acetyl β-D-glycosaminidase (NAG), serum IgA, clinical type, pathological grade, and immunopathology). The estimated glomerular filtration rate (eGFR) was counted according to the CKD-EPI equation developed by the American Chronic Kidney Disease Epidemiology Research Group [9].

2.1 Renal biopsy

Renal puncture was performed using a Menghini needle under the guidance of B-ultrasound, and 1 to 2 kidney tissues were punctured. The number of glomeruli in each specimen was greater than six.

2.2 Pathological examination and treatment methods

Specimens were fixed in formaldehyde, dehydrated and cleared in ethanol and xylene, embedded in paraffin, and cut into thin sections (approx. 2 to 3 μm). Specimens were routinely stained with hematoxylin and eosin (HE), Periodic Acid-silver Methenamine (PASM), and Masson. The HE staining was done in the following steps: paraffin sections were deparaffinized in xylene, rehydrated in ethanol, stained with hematoxylin, rinsed to remove excess stain, and differentiated in 0.7% hydrochloric acid - alcohol solution. Then, the rinsed sections turned blue. After stained with eosin, the sections were immersed in ethanol and carbolic acid-xylene solution and encapsulated with neutral resins. The PASM staining was done in the following steps: sections were deparaffinized and rehydrated, oxidized in 0.5% potassium permanganate solution for the first time and in 10% chromic acid for the second time, and rinsed with water; then, sections were treated with 1% aqueous sodium metabisulfite solution and rinsed with water again; subsequently, sections were microwaved in PASM working solution; after sections were taken out, they were rinsed with 0.1% aqueous gold chloride solution, stained with HE, and routinely dehydrated, cleared and encapsulated. The Masson staining was done in the following steps: sections were deparaffinized and rehydrated, fixed in Bouin's solution, slightly rinsed with running water, stained with celestine and hematoxylin, and again rinsed with water; then, sections were differentiated in 2% hydrochloric acid-alcohol solution and rinsed with water; subsequently, sections were stained with Ponceau-acid fuchsin solution and rinsed with distilled water; after that, sections were treated with phosphomolybdic acid solution, and counter-stained with aniline blue solution; stained sections were immersed in 1% glacial acetic acid and rinsed with alcohol; finally, they were routinely dehydrated, cleared and sealed.

2.3 Immune deposit examination and treatment methods

The punctured specimens were frozen, sectioned, and a standard fluorescein-labeled antibody was used for direct immunofluorescence. The specific procedures were to add drops of 0.01 mol/L pH7.4 phosphate buffered saline (PBS) on the sections; add drops of the properly-diluted fluorescein-labeled antibody solution to completely cover the sections; place the sections on slides; rinse the slides with 0.01 mol/L pH7.4 PBS, and soak sections three times with 0.01 mol/L pH7.4 PBS; remove the slides and use filter papers to absorb excess water; add buffered glycerin, and cover sections with coverslips. The results of fluoroscopy were quantified as (-), (+), (++), (+++), and (++++) on the basis of fluorescence intensity. Pathological grades were classified Types I to VI by reference to the Oxford classification method [8].

2.4 Clinical classification

According to the HSPN typing standard formulated by the Nephrology Group of Chinese Pediatric Society, Chinese Medical Association, HSPN types are divided into: type I: with hematuria or proteinuria; type II: with hematuria and proteinuria; type III: with acute nephritis; type IV: with nephrotic syndrome; type V: with acute nephritis; type VI: with chronic nephritis [10].

2.5 Grading and grouping by pathology of renal tubulo-interstitial lesions

The severity of renal tubulo-interstitial lesions was assessed by the semi-quantitative integration method [11]. Here are the assessment criteria: 1) Acute renal tubulo-interstitial lesions: The score is 0, 1, 2 and 3 respectively when the proportion of the area of interstitial mononuclear cell infiltration and cloudy swelling and renal tubular cloudy swelling and vacuolar degeneration to the total renal tubulo-interstitial area is 0, 1%-20%, 21%-50% and >50%. 2) Chronic renal tubulo-interstitial lesions: The score is 0, 1, 2 and 3 respectively when the proportion of the area of interstitial fibrosis and renal tubular atrophy to the total renal tubulo-interstitial area is 0, 1%-20%, 21%-50% and >50%. According to relevant references, the pathological grade of renal tubulo-interstitial lesions is 0 when the score is 0; grade 1 when the score is 1 to 3; grade 2 when the score is 4 to 6; grade 3 when the score is 7 to 9; grade 4 when the score is 10 to 12 [8].

Patients with pathological grade 0 (namely, without renal tubulo-interstitial lesions) were in Group A, patients with pathological grade 1 (namely, with mild renal tubulo-interstitial lesions) were in Group B, and patients with pathological grade 2 to 4 (namely, with moderate to severe renal tubulo-interstitial lesions) were in Group C.

2.6 Therapy

All three groups were treated with glucocorticoid, or glucocorticoid combined with immunosuppressive agents, depending on the results of renal biopsy.

2.7 Judgment of outcomes

Complete remission (CR) means the renal function is stable or improved after treatment, and UTP is not higher than 0.3g/24h. Partial remission (PR) means the renal function is stable or improved after treatment, and UTP decreases by more than half after treatment. Non-remission (NR) means UTP decreases by less than half after treatment. End-stage renal disease (ESRD) means patients develop chronic kidney disease stage V or needs dialysis due to decline in renal function.

2.8 Statistical analysis

The statistical analysis was performed using SPSS 17.0 software package. Continuous variables were presented as mean ± standard deviation ($\overline{x}$ ± sd), but abnormally-distributed continuous variables were presented as median (M) (P25-P75). Count data were presented as percentage or proportion (%). The correlation analysis of count data was $\chi 2$-tested. Statistical significance is set at $p < 0.05$.

3 Results

3.1 Baseline characteristics

A total of 148 patients aged 9-64 (averagely 33.2±16.4) were enrolled, including 86 males and 62 females, with a male to female ratio of 1.39:1. Among them, 25 patients (16.9%) were in group A, 105 patients (70.9%) in group B, and 18 patients (12.2%) in group C. HSPN in 90 cases (60.8%) occurred in winter and spring, and 22 cases had predisposing factors. Fifteen of them were triggered by upper respiratory tract infection, and the other 7 cases had a history of drug, food or other allergies. All patients had clinical manifestations of skin purpura. In terms of extrarenal manifestations, 37 cases were abdominal type (25.0%) and 27 cases were nodal type (18.2%). In 109 patients (73.6%), the eGFR obtained by the EPI formula was ≥90 $mL \cdot min^{-1} (1.73\ m^2)^{-1}$; in 21 patients (14.2%), the eGFR was 61-89 $mL \cdot min^{-1} (1.73\ m^2)^{-1}$; in 18 patients (12.2%), the eGFR was ≤60 $mL \cdot min^{-1} (1.73\ m^2)^{-1}$. There were no significant differences among the three groups in gender, age, extrarenal manifestations, haematological indexes, ESR, CRP, serum IgA, urinary β2 microglobulin, urinary NAG, and 24-hour urinary protein quantification (all $p > 0.05$). The eGFR of group B was lower than that of group A, and the difference was statistically significant ($p < 0.05$). The levels of serum creatinine and blood urea nitrogen in group C were higher than those in groups A and B, but the level of eGFR was lower, and the differences were statistically significant (all $p < 0.05$, Table 1).

3.2 Clinical types and pathological manifestations

In terms of clinical types, there were 25 cases of Type I-simple hematuria (16.9%), 9 cases of Type I-simple proteinuria (6.1%), 73 cases of Type II-hematuria and proteinuria (49.3%), 7 cases of Type III-acute nephritis (4.7%),

Table 1: Comparison of general data of each group.

Item	Group A	Group B	Group C	F/χ^2	p
Case (n, %)	25 (16.9)	105 (70.9)	18 (12.2)		
Male/female (case)	16/9	61/44	9/9	0.258	0.892
Age	34.2 ± 13.6	33.5 ± 8.9	36.4 ± 18.3	0.668	0.523
Winter and spring onset (n, %)	15 (60.0)	64 (60.9)	11 (61.1)	3.625	0.136
Incentives (n, %)					
Infection	3 (12.0)	10 (9.5)	2 (11.1)	5.651	0.069
Allergy	1 (4.0)	5 (4.8)	1 (5.6)	4.625	0.093
Extrarenal manifestations (n, %)					
Abdominal type	5 (20.0)	20 (19.0)	3 (16.7)	4.256	0.103
Articulated	3 (12.0)	19 (18.1)	3 (16.7)	3.264	0.169
Blood index					
Blood leukocyte (109/L)	10.9 ± 5.3	9.4 ± 4.6	9.1 ± 4.2	0.625	0.586
Hemoglobin (g/L)	133.5 ± 19.7	133.4 ± 18.9	131.9 ± 20.6	0.369	0.751
Platelet (109/L)	229.6 ± 70.2	224.7 ± 70.1	226.3 ± 72.6	0.450	0.614
Urine protein quantification (g/24h)	2.9 ± 2.6	2.8 ± 2.2	3.1 ± 2.3	0.698	0.496
Creatinine (μmol/L)	66.2 ± 40.1	70.1 ± 35.6	103.6 ± 63.5ab	128.652	0.001
Urea nitrogen (mmol/L)	5.6 ± 4.8	6.2 ± 5.3	10.2 ± 4.6ab	103.369	0.000
eGFRmL·min-1(1.73 m2)-1	157.2 ± 50.8	114.6 ± 36.5a	80.3 ± 36.4ab	136.489	0.000
Blood sedimentation (mm/h)	11.8 ± 8.9	13.5 ± 10.2	14.7 ± 12.3	0.631	0.526
C-reactive protein (mg/L)	6.5 ± 9.6	7.7 ± 10.3	8.1 ± 9.5	0.463	0.601
Serum IgA (mg/L)	24.6 ± 9.2	30.2 ± 10.4	31.4 ± 24.9	0.708	0.520
Urinary β2-microglobulin (μg·L-1)	159.2 (59.2, 405.3)	90.3 (53.9, 174.3)	76.9 (27.4, 277.6)	0.694	0.503
Urinary NAG (U·L-1)	29.6 (8.3, 32.9)	11.6 (6.5, 21.3)	12.9 (7.6, 64.9)	0.584	0.587

Compared with group A, [a]$p < 0.05$; compared with group B, [b]$p < 0.05$. NAG, N-acetyl β-D-glycosaminidase.

27 cases of Type IV-nephrotic syndrome (18.2%), 2 cases of Type V-acute nephritis (1.4%), and 5 cases of Type VI-chronic nephritis (3.4%).

In terms of pathological manifestations, there was no statistically significant difference among the three groups in the distribution of pathological types and the proportion of crescents (both $p > 0.05$), but the proportion of glomerulosclerosis in group C was higher than that in groups A and B ($p < 0.05$). In terms of pathological types, there were 7 cases of Type I (4.7%), 31 cases of Type II (21.0%), 100 cases of Type III (67.6%), 7 cases of Type IV (4.7%), 0 case of Type V (0%), and 3 cases of Type VI (2.0%).

In terms of immunopathological types, there were 18 cases of IgA deposition (12.2%), 46 cases of IgA + IgM deposition (31.1%), 17 cases of IgA + IgG deposition (11.4%), and 67 cases of IgA + IgG + IgM deposition (45.3%) (Table 2).

3.3 Correlation between clinical types and pathological types

Clinical type II or above generally corresponded to pathological type II or above. However, 22 cases were clinical type I but pathological type III or above, and 5 cases were pathological type II or below but clinical type IV or V. The chi-square test was performed on the overall composition of pathological types in different clinical types ($\chi^2 = 0.252$, $p = 0.002$). The results indicated that the overall composition of pathological types varied in different clinical types. The correspondence analysis found that clinical type II was closely correlated with pathological types II and IIIa; pathological type IV was closely correlated with clinical type VI; pathological type IIIb was closely correlated with clinical type IV; but other pathological types were not closely correlated with clinical types (Figure 1).

Table 2: Comparison of clinical manifestations and pathological types in each group.

Item	Group A	Group B	Group C	F/χ^2	p
Clinical manifestations				0.421	0.796
I	5	25	4		
II	12	53	8		
III	2	4	1		
IV	4	20	3		
V	1	1	0		
VI	1	2	2		
Pathological type				0.436	0.803
I	2	4	1		
II	4	25	2		
III	15	72	13		
IV	3	3	1		
V	0	0	0		
VI	1	1	1		
Glomerular sclerosis ratio (%)	6.1 ± 9.7	5.4 ± 7.8	8.9 ± 11.9ab	110.692	0.002
Crescent moon Ratio (%)	7.2 ± 11.3	9.5 ± 12.8	10.8 ± 13.1	0.265	0.436
Immunophenotyping				0.436	0.821
IgA deposition alone	3	14	1		
IgA + IgM deposition	8	34	4		
IgA + IgG deposition	2	13	2		
IgA + IgG + IgM deposition	12	44	11		

Compared with group A, $^{a}p < 0.05$; compared with group B, $^{b}p < 0.05$.

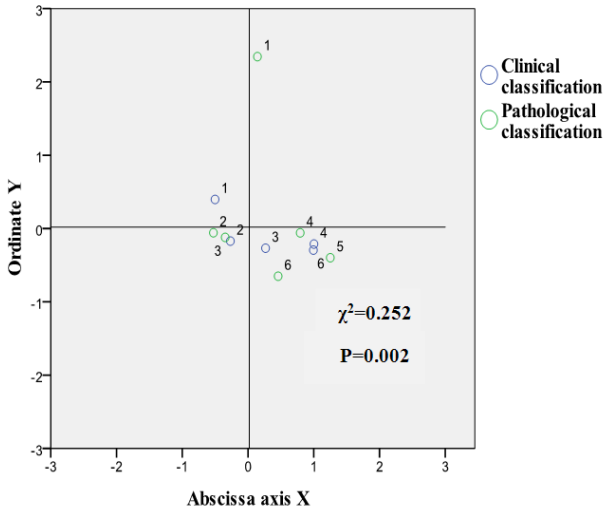

Figure 1: Corresponding analysis of clinical type and pathological type. According to pathological type (I = 1, II = 2, IIIa = 3, IIIb = 4, IV = 5, VI = 6) and clinical classification (I = 1, II = 2, III = 3, IV = 4, V = 5, VI = 6). After the data is assigned, the corresponding analysis is used, χ2 = 0.252, p = 0.002.

3.4 Severity of hematuria and glomerular lesions

Clinical US-Mi results showed statistically significant differences among the three groups in the number of red blood cells in urinary sediment (χ^2 = 0.028, p = 0.003, Table 3).

3.5 Prognosis and outcome of different groups

In terms of prognosis and outcome, there were 12 cases of CR, 11 cases of PR, and 2 cases of NR in group A; there were 36 cases of CR, 35 cases of PR, and 33 cases of NR in group B; 3 cases in group C and 1 case in group B developed ESRD. There was a statistically significant difference in prognosis among the three groups (χ^2 = 18.561, p = 0.000), and the prognosis of patients with moderate to severe

Table 3: Relationship between renal tubular injury and red blood cell count in urine sediment.

Item	Urinary sediment red blood cell count	χ2	p
Group A (n = 25)	48.60 (6.00-265.97)		
Group B (n = 105)	72.65 (18.15-369.67)a	0.028	0.003
Group C (n = 18)	266.00 (42.25-1,150.48)ab		

Compared with group A, [a]p<0.05; compared with group B, [b]p < 0.05.

renal tubulo-interstitial lesions in group C was worse than that of others (Table 4).

4 Discussion

The most common clinical manifestation of HSP is purpura in the skin and mucous membranes, which can be accompanied by abdominal pain and joint pain. HSPN is a serious complication and is difficult to control clinically [12]. Studies have found that the incidence of HSPN fluctuates between 20% and 80% [13,14]. Renal failure occurs in approximately 1%-12% patients with HSPN [15]. Previous studies have found that the incidence of HSPN is higher in the winter and spring, and is higher in men than in women, and this disease is most probably triggered by infection, which is in line with the findings of this study [16,17].

Previous studies also found that for most HSPN patients with renal interstitial lesions, the majority of lesions were mild lesions; this study found that 105 cases had mild lesions (70.9%), and 18 cases had moderate to severe lesions (12.2%), which is in line with the findings of previous studies [18]. Lim et al. found that the severity of renal tubulo-interstitial lesions was not correlated with gender, age, clinical manifestations, and biochemical tests, which is largely in line with the findings of this study [19]. A study pointed out that urinary β2 microglobulin and urinary NAG levels were correlated with renal tubulo-interstitial lesions, which is not in line with the findings of this study [20]. We believe that the above two indicators cannot reflect the severity of renal tubulo-interstitial lesions and kidney biopsy is still required for definitive diagnosis. This study also found that patients with severe renal tubulo-interstitial lesions had a higher proportion of glomerulosclerosis and worse renal function and glomerular filtration rate than patients with mild to moderate renal tubulo-interstitial lesions. The possible reason was revealed in the study of Hodgkins et al.: renal tubulo-interstitial lesions can affect glomerular filtration through the glomerulotubular feedback mechanism and further aggravate glomerular injury, also, the glomerular injury and glomerulosclerosis can result in decrease in nephrons, high filtration of residual nephrons, and ischemia and hypoxia, which in turn aggravate renal tubular lesions [21].

In terms of clinical and pathological studies, this study found that clinical type II was the most common, and pathological type IIIa was the most common. The correspondence analysis found that: clinical type II was closely correlated with pathological types II and IIIa; pathological type IV was closely correlated with clinical type VI; pathological type IIIb was closely correlated with clinical type IV; but other pathological types were not closely correlated with clinical types. Therefore, this study believes that clinical grading cannot be used to judge the severity and prognosis of the disease, and further biopsy is needed for comprehensive judgment of pathological type.

This study examined the severity of hematuria and renal tubular lesion and found that the number of red blood cells in urinary sediment was significantly higher in patients with moderate to severe renal tubulo-interstitial lesions than in patients with mild tubulo-interstitial lesions, and that the severity of renal tubulo-interstitial lesions was correlated with the severity of hematuria, suggesting a difference in the severity of hematuria among

Table 4: Prognosis of the three groups after follow-up in 5 years after treatment.

Outcome	Group A (n = 25)	Group B (n = 105)	Group C (n = 18)	χ^2	p
Complete relief	12 (48.0)	36 (34.3)a	4 (22.2)ab		
Partial relief	11 (44.0)	35 (33.3)a	5 (27.8)ab	18.561	0.000
Not relieved	2 (8.0)	33 (31.4)a	6 (33.3)a		
End-stage renal disease	0	1 (1.0)a	3 (16.7)ab		

Compared with group A, [a]p < 0.05; compared with group B, [b]p < 0.05.

patients with different severity of renal tubulo-interstitial lesions. Renal tubular lesion can promote inflammatory cell infiltration, which is line with the findings of the previous studies, that is, the main cause of hematuria is the interaction with inflammatory mediators leading to vascular endothelial injury [21-24].

Previous study found that most patients had a good prognosis, and the incidence of ESRD was 1%-5% [3]. However, another study suggested that 20%-30% of HSPN patients progressed to ESRD [25]. The incidence of ESRD in this study was 2.7%, which is in line with the findings of the former. Studies have found that renal tubulo-interstitial lesions and glomerular injury are reversible [19]. Treatment of patients with severe renal impairment with hormones and immunosuppressive agents can improve prognosis, but renal tubulo-interstitial lesions may still progress. For lupus nephritis, it is common that the glomerular and tubular injury is visually reflected by repeated biopsy, which is a good indicator for the monitoring of lupus nephritis [26]. For HSPN patients whose condition changes or relapses, repeated renal biopsy helps realize early detection and intervention of renal tubulo-interstitial lesions, which can improve the prognosis of patients to some extent.

In summary, HSPN frequently occurs in winter and spring, and is most probably triggered by infection. Clinical type II is the most common cause; pathologically, type IIIa is more common. The severity of renal tubulo-interstitial injury is positively correlated with the decline in renal function and GFR, and is correlated with the severity of hematuria. Most patients with HSPN have a good prognosis, but those with severe renal tubulo-interstitial lesions have a poor prognosis. For this reason, patients may be re-examined by renal biopsy when necessary, so that an appropriate early therapy can be applied to improve the prognosis.

Conflicts of interest: Authors state no conflict of interest.

References

[1] Johnson, E. F., Wetter, D. A., Lehman, J. S., Hand, J. L., Davis, D. M., Tollefson, M. M. Leukocytoclastic vasculitis in children: clinical characteristics, subtypes, causes and direct immunofluorescence findings of 56 biopsy-confirmed cases. J Eur Acad Dermatol Venereol, 2017, 31, 544-549

[2] Rai, A., Nast, C., Adler, S. Henoch-Schönlein purpura nephritis. J Am Soc Nephrol, 1999, 10, 2637-2644

[3] Pohl, M.. Henoch-Schonlein purpura nephritis. Pediatr Nephrol, 2015, 30, 245-252

[4] Assadi, F. Childhood Henoch-Schonlein nephritis: a multivariate analysis of clinical features and renal morphology at disease onset. Iran J Kidney Dis, 2009, 3, 17-21

[5] Yong, A. M., Lee, S. X., Tay, Y. K. The profile of adult onset Henoch-Schonlein purpura in an Asian population. Int J Dermatol, 2015, 54, 1236-1241

[6] Nickavar, A., Mehrazma, M., Lahouti, A. Clinicopathologic correlations in Henoch-Schonlein nephritis. Iran J Kidney Dis, 2012, 6, 437-440

[7] Kawasaki, Y., Suzuki, J., Sakai, N., Nemoto, K., Nozawa, R., Suzuki, S., Suzuki, H. Clinical and pathological features of children with Henoch-Schoenlein purpura nephritis: risk factors associated with poor prognosis. Clin Nephrol, 2003, 60, 153-160

[8] Cattran, D. C., Coppo, R., Cook, H. T., Feehally, J., Roberts, I. S., Troyanov, S., et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int, 2009, 76, 534-545

[9] Jia, Z., Zhou, Y., Liu, X., Wang, Y., Zhao, X., Wang, Y., et al. Comparison of different anthropometric measures as predictors of diabetes incidence in a Chinese population. Diabetes Res Clin Pract, 2011, 92, 265-271

[10] Chinese Medical Association Pediatrics Section Nephrology Unit. Clinical classification, diagnosis and treatment of glomerular diseases in children. Zhonghua Er Ke Za Zhi (Chin J Pediatr), 2001, 39, 746-749

[11] Foster, B. J., Bernard, C., Drummond, K. N., Sharma, A. K. Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. J Pediatr, 2000, 136, 370-375

[12] Li, X., Ma, J., Zhao, Y., Wang, H. Y., Li, X. M. Development of Crescentic Immunoglobulin A Nephritis and Multiple Autoantibodies in a Patient during Adalimumab Treatment for Rheumatoid Arthritis. Chin Med J (Engl), 2015, 128, 2555-2556

[13] Komatsu, H., Fujimoto, S., Yoshikawa, N., Kitamura, H., Sugiyama, H., Yokoyama, H. Clinical manifestations of Henoch-Schonlein purpura nephritis and IgA nephropathy: comparative analysis of data from the Japan Renal Biopsy Registry (J-RBR). Clin Exp Nephrol, 2016, 20, 552-560

[14] Chang, H., Cao, Y., Lin, Y. I., Zhu, H., Fu, Y., Chen, X., et al. Association between toll-like receptor 6 expression and auxiliary T cells in the peripheral blood of pediatric patients with allergic purpura. Exp Ther Med, 2015, 10, 1536-1540

[15] Zhong, W., Zhou, T. B., Jiang, Z. Association of endothelial nitric oxide synthase gene polymorphism with the risk of Henoch-Schonlein purpura/Henoch-Schonlein purpura nephritis. Ren Fail, 2015, 37, 372-376

[16] Garcia-Porrua, C., Calvino, M. C., Llorca, J., Couselo, J. M., Gonzalez-Gay, M. A. Henoch-Schonlein purpura in children and adults: clinical differences in a defined population. Semin Arthritis Rheum, 2002, 32, 149-156

[17] Kikuchi, Y., Yoshizawa, N., Oda, T., Imakiire, T., Suzuki, S., Miura, S. Streptococcal origin of a case of Henoch-Schoenlein purpura nephritis. Clin Nephrol, 2006, 65, 124-128

[18] Feng, D., Huang, W. Y., Hao, S., Niu, X. L., Wang, P., Wu, Y., et al. A single-center analysis of Henoch-Schonlein purpura nephritis with nephrotic proteinuria in children. Pediatr Rheumatol Online J, 2017, 15, 15

[19] Lim, B. J., Shin, J. I., Choi, S. E., Rhim, H., Lee, J. S., Kim, P. K.,et al. The significance of tubulointerstitial lesions in childhood Henoch-Schonlein nephritis. Pediatr Nephrol, 2016, 31, 2087-2093
[20] Mise K, Hoshino J, Ueno T, Hazue, R., Hasegawa, J., Sekine, A., et al. Prognostic Value of Tubulointerstitial Lesions, Urinary N-Acetyl-beta-d-Glucosaminidase, and Urinary beta2-Microglobulin in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy. Clin J Am Soc Nephrol, 2016, 11, 593-601
[21] Hodgkins, K. S., Schnaper, H. W. Tubulointerstitial injury and the progression of chronic kidney disease. Pediatr Nephrol, 2012, 27, 901-909
[22] Ding, G. X., Wang, C. H., Che, R.C., Guan, W. Z. Yuan, Y. G., Su, M., et al. Heat shock protein 70-2 and tumor necrosis factor-alpha gene polymorphisms in Chinese children with Henoch-Schonlein purpura. World J Pediatr, 2016, 12, 49-54
[23] Sahip, B., Pamuk, G. E., Uyanik, M. S., Pamuk, O. N. Higher interleukin 21 level is predictive of relapse in immune thrombocytopenia. Is it associated with activation of the complement system? Br J Haematol, 2016, 173, 321-323
[24] Chen, J. Y., Mao, J. H. Henoch-Schonlein purpura nephritis in children: incidence, pathogenesis and management. World J Pediatr, 2015, 11, 29-34
[25] Davin, J. C., Coppo, R. Henoch-Schonlein purpura nephritis in children. Nat Rev Nephrol, 2014, 10, 563-573
[26] Pagni, F., Galimberti, S., Galbiati, E., Rebora, P., Pietropaolo, V., Pieruzzi, F., et al. Tubulointerstitial lesions in lupus nephritis: International multicentre study in a large cohort of patients with repeat biopsy. Nephrology (Carlton), 2016, 21, 35-45