Original article

Clinicopathological features and prognosis of membranoproliferative-like Henoch-Schönlein purpura nephritis in children

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Background: **The aim of this retrospective study was to define the clinical manifestations, pathological features and prognosis of children with membranoproliferative-like Henoch-Schönlein purpura nephritis (HSPN), representing International Study of Kidney Disease in Children (ISKDC) grade VI.**

Methods: **Among 245 patients with HSPN treated in our hospital between 2008 and 2010, nine patients (3.7%) were diagnosed with HSPN of ISKDC grade VI (males=5, females=4, age: 9.5±2.03 years, mean±SD). The clinical features, laboratory and pathological findings, treatment and outcome of the 9 patients were retrospectively analyzed.**

Results: **Of the 9 patients, 7 (78%) presented with hematuria and nephrotic syndrome, and were treated with steroids (oral prednisone or intravenous methylprednisolone pulse therapy) and immunosuppressants (oral tripterygium glycosides or intravenous cyclophosphamide pulse therapy). One (11%) patient had hematuria and nephrotic range proteinuria (>50 mg/kg per 24 hours) and was treated with oral prednisone and tripterygium glycosides. Another (11%) patient presented with hematuria and moderate proteinuria (25-50 mg/kg per 24 hours) and was treated with oral tripterygium glycoside only. Histopathological examination showed diffuse glomerular mesangial and endocapillary proliferation, mesangial interposition, double-contour formation, podocyte hypertrophy, shedding, and cytoplasmic absorption droplets. The percentages of glomeruli with small cellular crescents varied from 4%-25% in 6 of 9 patients. Follow-up for 2 to 4 years showed excellent recovery in all patients.**

Conclusions: **The main clinical feature of ISKDC grade VI HSPN in children is a nephrotic syndrome with hematuria. The excellent prognosis of the disease was probably related to early diagnosis and treatment with steroids and/or immunosuppressants, and mild degree of glomerulosclerosis and tubulointerstitial damage.**

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Key words: **clinicopathological features; Henoch-Schönlein purpura nephritis; prognosis**

Introduction

Henoch-Schönlein purpura (HSP) in children is an IgA-mediated multi-system vasculitis that predominantly involves the skin, joints, gastrointestinal tract, and kidneys.[1-3] Renal involvement is the main cause of morbidity and mortality in children with HSP.[4,5] The severity of histopathological changes in HSP nephritis (HSPN) is classified by the International Study of Kidney Disease in Children (ISKDC) into six categories:[6] grade I: minimal alterations; grade II: mesangial proliferation; grade III: (a) focal or (b) diffuse mesangial proliferation or sclerosis with <50% crescents; grade IV: (a) focal or (b) diffuse mesangial proliferation or sclerosis with 50%-75% crescents; grade V: (a) focal or (b) diffuse mesangial proliferation or sclerosis with >75% crescents; and grade VI: membranoproliferative-like lesion. Lesions of the latter grade show mesangial and endocapillary proliferation with diffuse double contour of the capillary walls and mesangial cell interposition.

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Grade VI HSPN is uncommon with a reported incidence of 1.1% to 8.6%,[6-10] and has been reported in several series and a few case reports.[11,12] Both full recovery and progression to death or renal insufficiency have been reported.[6] Therefore, the prognostic values of renal clinical symptoms and histopathological lesions in patients with grade VI HSPN remain to be clarified. Any pathological documentation should include factors that may provide prognostic information. In this study, we analyzed in detail the clinicopathological features and outcomes of nine children with grade VI HSPN.

Methods

Patient selection and clinical parameters

We reviewed the records of 9 patients with grade VI HSPN from the 245 HSPN patients who had undergone renal biopsy at our hospital between 2008 and 2010. The diagnosis of HSP was based on the criteria of the American College of Rheumatology[13] and a new international classification of childhood vasculitis.[14] All nine patients presented with palpable purpura, hematuria and proteinuria, with or without gastrointestinal symptoms and/or arthritis, but none had thrombocytopenic purpura. Patients with other systemic diseases were excluded. Renal specimens that included ≥15 glomeruli were available in the 9 patients. The study protocol was approved by the Human Ethics Review Committee of our hospital and a signed consent form for renal biopsy was obtained from the parents of the patients.

The clinical features selected for analysis included age, sex, palpable purpura, edema, abdominal pain, arthritis or arthralgia, proteinuria, and hematuria. The following parameters were retrieved from the medical records: blood urea nitrogen (BUN), serum creatinine (sCr), estimated glomerular filtration rate (eGFR) (calculated by the formula: [(Urine creatinine×24-hour urine volume)/(serum creatinine×1440)]×[1.73 (m^2)/body surface area (m^2)]), IgA, complement C3, complement C4, anti-nuclear antibodies (ANAs) and systolic and diastolic blood pressure (SBP and DBP). The values of the above parameters measured at or near the time of renal biopsy were used for analysis.

Microscopic hematuria was defined as the presence of ≥25 red blood cells/mm^3. Proteinuria was categorized as mild (<25 mg/kg per day), moderate (25-50 mg/kg per day), and nephrotic range proteinuria (≥50 mg/kg per day). Nephrotic syndrome (NS) represented the presence of proteinuria of >50 mg/kg per day, with a serum albumin level of ≤25 g/L. As a control, we also estimated the incidence of NS and tubulointerstitial fibrosis in the 245 patients with HSPN. The 9 patients with grade VI HSPN were followed up for 2 to 4 years, and the outcome was graded according to the classification of Counahan[6] into: A: Normal: the patient was normal on physical examination, with normal urinary and renal function; B: Minor urinary abnormality: the patient was normal on physical examination, with microscopic hematuria or proteinuria <1 g per day (or <40 mg/h per m^2), or both; C: Active renal disease: proteinuria >1 g per day (>40 mg/h per m^2), hypertension (SBP and/or DBP >95th percentile on 3 occasions over weeks), or both, and GFR >60 mL/min per 1.73 m^2; and D: renal insufficiency: eGFR <60 mL/min per1.73 m^2 or death.

Assessment of renal histopathological changes

Renal biopsy was performed within 1-2 months after the onset of HSPN. Specimens of renal tissue were sectioned, stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, and silver methenamine, and examined under a light microscope. For immunofluorescence examination, a portion of the renal specimen was frozen and exposed to fluorescein isothiocyanate (FITC)-conjugated anti-human IgA, IgG, IgM, C3, C4, Clq and fibrinogen. All antibodies were obtained from Dako (Glostrup, Denmark). The biopsy sections were independently examined and evaluated by two renal pathologists blinded to the clinical information. HSPN was classified in all patients as ISKDC grade I-VI HSPN. The percentages of glomeruli that showed mesangial proliferation, endothelial proliferation, double contour, podocyte hypertrophy, glomerular sclerosis and crescent were counted separately. Mesangial proliferation, endothelial proliferation, and crescent were scored according to the formal and simpler scoring system in Oxford classification of IgA nephropathy.[15,16] Tubulointerstitial damage in the renal biopsy specimen was also scored semiquantitatively using the scoring system of Andreoli and Bergstein for IgA nephropathy[17] and modified by Foster et al.[18] Acute tubulointerstitial lesions included interstitial mononuclear infiltrates, interstitial edema, and tubulitis, and the scores of these three factors were combined into the acute tubulointerstitial lesion score. Chronic tubulointerstitial lesions included tubular atrophy and interstitial fibrosis. The severity of tubulointerstitial damage was graded into grade 0 (no obvious change), grade 1 (lesions involving <25% of the area), grade 2 (lesions affecting ≥25 to 50%), and grade 3 (lesions involving ≥50%).

Treatment strategy

In this series, patients with moderate proteinuria (25-50 mg/kg per day) and hematuria were treated with oral tripterygium glycosides, whereas those with

nephrotic range proteinuria (≥50 mg/kg per day, and serum albumin level >25 g/L) and hematuria received oral tripterygium glycosides and prednisone. Among the 7 patients with NS (>50 mg/kg per day and serum albumin ≤25 g/L) and hematuria, 4 received oral tripterygium glycosides and prednisone, 1 received oral tripterygium glycosides, intravenous methylprednisolone pulse therapy, followed by oral sufficiency prednisone, and 2 received intravenous methylprednisolone and cyclophosphamide pulse therapy, followed by oral sufficiency prednisone. Tripterygium glycosides (1-1.5 mg/kg per day) was administered for a mean duration of 3 months (range 2-4 months) and tapered off 1-3 months. Tripterygium glycosides, the major active component of tripterygium wilfordii Hook F, has potent immunosuppressive effects, and has been used only in China for the treatment of glomerulonephritis for more than 30 years with dramatic antiproteinuric effects.[19-22] Prednisone (1-2 mg/kg per day, maximum dose ≤60 mg/day) was administered in three divided doses for 4 weeks, followed by a single dose of 1-2 mg/kg on alternative days for 4 weeks and continued for 3-5 months with subsequent tapering of the dose. Methylprednisolone pulse therapy was used at a dose of 15-30 mg/kg per day (maximum 1 g) for 3 days, then followed by oral sufficiency prednisone. Cyclophosphamide (8-12 mg/kg per day, for 2 days) intravenous pulse therapy was provided with a 2-week rest interval for 4 treatment courses, followed by monthly therapy for 2-4 courses of treatment (total dose ≤150 mg/kg). No apparent side effects of cyclophosphamide and tripterygium glycosides were observed (e.g., myelosuppression, hepatic insufficiency, or hemorrhagic cystitis). Each patient was also treated with anti-platelet agents, anti-coagulants, and angiotensin converting enzyme inhibitor (ACEI).

Results

Clinical features

All 9 patients, 5 boys and 4 girls, aged between 7 and 11 years, presented with palpable purpura and abdominal pain. Six of these patients also had arthritis or arthralgia. Moreover, one patient (11.11%) presented with moderate proteinuria (37.4 mg/kg per day) and hematuria, one (11.1%) with nephrotic range proteinuria (54.6 mg/kg per day) and hematuria, 7 (77.78%) with NS and hematuria, and 4 with edema (Tables 1&2). Six patients had macroscopic hematuria, but 3 had microscopic hematuria (Table 2). The levels of sCr, IgA, C3, C4, ANAs, SBP, and DBP were within normal

Table 1. Clinical features of the nine children with ISKDC grade VI Henoch-Schönlein purpura nephritis

Case no.	Age (y)	Palpable purpura	Abdominal pain	Arthritis or arthralgia	Edema	Nephrotic syndrome	SBP/DBP (mmHg)	BUN (mmol/L)	sCr (μmol/L)	IgA (g/L)	C3 (g/L)	C4 (g/L)	ANAs
1	11	+	+	+	+	+	120/80	3.9	40	1.827	0.76	0.32	-
2	7	+	+	+	+	+	100/70	8.6	61	0.766	0.74	0.22	-
3	9	+	+	+	-	+	100/70	2.5	39	1.464	0.99	0.19	-
4	10	+	+	-	-	-	110/70	2.8	51	1.723	1.14	0.35	-
5	11	+	+	+	-	+	101/70	3.3	45	1.962	1.01	0.23	-
6	7	+	+	-	+	+	85/60	3.9	53	1.52	0.88	0.35	-
7	8	+	+	+	+	+	95/70	6.9	53	2.288	1.17	0.33	-
8	10	+	+	+	-	+	100/70	4.5	46	1.183	1.48	0.20	-
9	9	+	+	-	-	-	110/70	4.1	49	1.11	0.91	0.10	-

Normal IgA level: low limits 0.44-0.61 g/L, high limit 3.45-3.95 g/L; normal C3 level: 0.70-2.06 g/L; normal C4 level: 0.11-0.61 g/L. SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: blood urea nitrogen; sCr: serum creatinine; ANAs: anti-nuclear antibodies.

Table 2. Changes in proteinuria and hematuria and follow-up findings in the nine patients of the present study

Case no.	Proteinuria (mg/kg/24 h)			Macroscopic (Y/N)/microscopic (RBC/mm^3) hematuria			eGFR (mL/min/1.73 m^2)		Follow-up (y)	Prognosis
	Baseline	Last	Time to resolution (mon)	Baseline	Last	Time to resolution (mon)	Baseline	Last		
1	75.7	2.8	2	Y/4512	N/12	5	101	108.8	4	A
2	52.1	2.7	3	Y/3200	N/24	4	75.5	102.9	4	A
3	54.4	5.5	3	Y/1581	N/7	6	91.4	101.4	3	A
4	37.4	2.9	15	Y/4392	N/6	16	104.6	95.0	2.5	A
5	69.1	2.2	3	Y/513	N/24	6	110.0	108.0	2.5	A
6	60.8	3.3	1.5	N/210	N/1	4	82.7	119.2	2.5	A
7	189.8	6.2	3	Y/2115	N/13	18	91.5	115.5	2.5	A
8	114.5	2.1	3	N/151	N/18	12	112.8	114.8	2.5	A
9	54.6	2.2	3	N/327	N/4	7	157.2	117.5	2	A

A: normal findings on physical examination, together with normal urine and renal function tests; RBC: red blood cell; eGFR: estimated glomerular filtration rate.

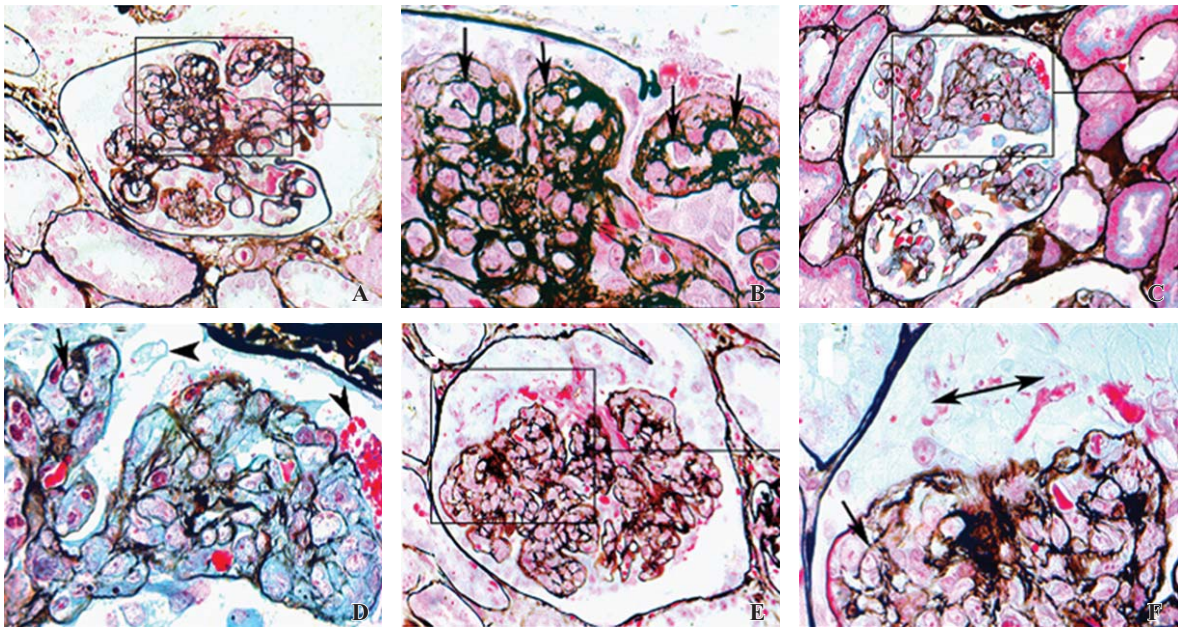

Fig. 1. Pathological features of ISKDC grade VI Henoch-Schönlein purpura nephritis. Boxed areas in **A, C&E** are shown at higher magnifications in **B, D&F**, respectively. **A**: Mesangial and endocapillary proliferation, mesangial interposition and double-contour formation in the glomeruli; **B**: Glomerular basement membrane (GBM) (arrows); **C**: Representative glomerulus with podocyte hypertrophy and cytoplasmic absorption droplets in podocyte, based on mesangial interposition and double-contour formation; **D**: arrow: GBM, arrowheads: hypertrophy and shedding podocyte and cytoplasmic absorption droplets in the podocytes; **E**: Segmental cellular crescent formation, based on mesangial interposition and double-contour formation; **F**: arrow: GBM, double arrow: cellular crescent. Silver methenamine staining with Masson counterstaining (**A, C&D**: original magnification × 400; **B, D&F**: original magnification × 1000).

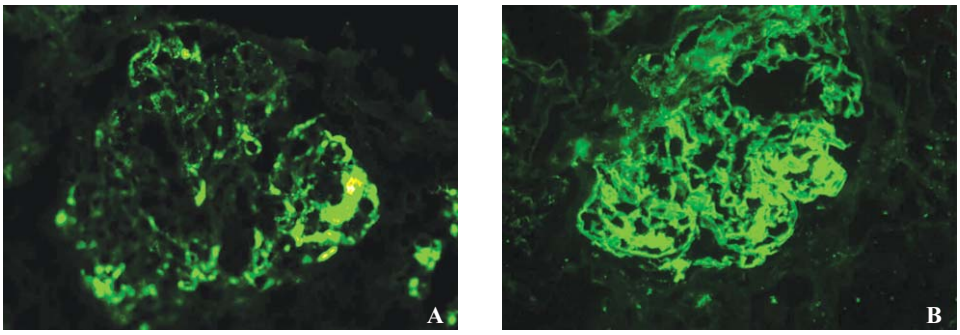

Fig. 2. IgA and fibrinogen deposition in membranoproliferative-like garland pattern. **A**: representative immunofluorescence staining for IgA. The granular pattern in the mesangial region and segmental pattern along the capillary walls; **B**: fibrinogen deposition in the mesangium and glomerular capillary walls (original magnification × 400).

ranges in all patients, whereas 2 patients had a transient rise in BUN, and 1 patient had mildly low eGFR (75.5 mL/min per 1.73 m^2) (Tables 1&2).

Table 2 shows the incidence of NS according to ISKDC grades in the 245 patients. NS was diagnosed in 78% of the patients with ISKDC grade VI HSPN, which was higher than that of patients with grade IV HSPN (56%), but lower than that of those with grade V HSPN (100%).

Histopathological features

The mean number of glomeruli included in the renal biopsy specimens was 33 (range: 16-56). All cases showed diffuse mesangial cell proliferation with matrix accumulation (Fig. 1), segmental mesangial interposition and double contour formation (Fig. 1), podocyte hypertrophy (Fig. 1C&D), and varied degrees of endothelial cell proliferation and inflammatory cells infiltration. Small cellular crescent (<50% Bowman's capsule was involved) formation was noted in 6 of the 9 specimens (Fig. 1E&F), the percentages of glomeruli with this feature varied from 4.2% to 25% (mean, 15.2% of all specimens). Table 3 illustrates the rate of tubulointerstitial fibrosis according to the ISKDC grade in the 245 patients. Tubulointerstitial fibrosis was most common in ISKDC grade IV (78%), followed by grade

Table 3. Nephrotic syndrome and tubulointerstitial fibrosis according to ISKDC grade in 245 patients

	ISKDC histology grades							
	I	II		III		IV	V	VI
		IIa	IIb	IIIa	IIIb			
No. of patients	2	34	23	114	52	9	2	9
Nephrotic syndrome	0	1 (2.9%)	4 (17.4%)	15 (13.2%)	15 (28.8%)	5 (55.6%)	2 (100%)	7 (77.8%)
Tubulointerstitial fibrosis	0	0 (0%)	2 (8.7%)	7 (6.1%)	25 (48.1%)	7 (77. 8%)	1 (50%)	2 (22.2%)

Table 4. Histopathological findings in the nine patients with ISKDC grade VI Henoch-Schönlein purpura nephritis

Case no	Number of glomeruli	Mesangial proliferation			Double-contour in formation %	Endothelial proliferation		Podocyte in hypertrophy	Cell crescent		Glomerular Sclerosis	Tubulointerstitial lesions	
		%	Formal score	Simpler score		%	Simpler score	%	%	Score	%	Acute	Chronic
1	25	64	0.75	M1	64	52	E1	52	16	0.36	0	0	0
2	40	100	-*	-*	100	100	E1	100	15	0.40	0	1	0
3	33	63	1.54	M1	57	20	E1	20	24	0.55	0	1	0
4	56	73	1.61	M1	62	32	E1	36	18	0.48	0	1	0
5	47	74	1.61	M1	74	39	E1	7.5	4	0.04	0	1	1
6	28	67	1.59	M1	54	21	E1	16	0	0	2	1	0
7	32	100	2	M1	54	12	E1	32	25	0.72	0	1	0
8	32	63	1.42	M1	56	23	E1	36	0	0	3	1	1
9	16	62	1.91	M1	53	31	E1	62	0	0	0	1	0

The scores of mesangial proliferation and crescent formation were based on Oxford classification of IgA nephropathy.[15] M0: less than half the glomeruli have more than three cells in a mesangial area; M1: more than half of the glomeruli have more than three cells in a mesangial area; E0: absence endothelial proliferation; E1: present endothelial proliferation.[16] *: The mesangial area showed endothelial proliferation, making it difficult to score mesangial proliferation based on Oxford classification of IgA nephropathy.[15]

Table 5. Immunofluorescence findings in the nine patients of the present study

Label	*n*	Positive patterns
IgA	9	Positive staining located in diffuse mesangial regions and segmental capillary walls, three cases showed "garland" pattern.
Fibrinogen	9	Positive staining located in diffuse mesangial regions and segmental capillary walls
C3	4	Positive staining located in diffuse mesangial regions
IgM	4	Positive staining located in diffuse mesangial regions and segmental capillary walls
IgG	1	Positive staining located in diffuse mesangial regions and segmental capillary walls
C1q	1	Positive staining located in diffuse mesangial regions and segmental capillary walls
C4	1	Positive staining located in diffuse mesangial regions and segmental capillary walls

V (50%), and least in grade VI HSPN (22%). Acute tubulointerstitial lesion score 1 was seen in 8 patients, and 2 patients showed mild chronic tubulointerstitial lesions. Table 4 shows the histopathological changes observed in the 9 patients with ISKDC grade VI HSPN.

Immunofluorescence studies

IgA (Fig. 2A) and fibrinogen (Fig. 2B) deposition was evident in all 9 patients, and these changes were mainly observed in the mesangium and segmentally in the capillary walls, while membranoproliferative-like garland pattern was noted in 3 patients. The deposition of C3 and IgM, especially in the mesangium, was noted in some patients. The deposition of IgG, C4 and C1q in the mesangium and segmentally in the capillary walls was occasionally seen in 1 patient. The results of immunofluorescence microscopic observation are summarized in Table 5.

Clinical outcome

The 24-hour urinary protein excretion was significantly decreased to less than 150 mg with no protein on urine dipstick within 3 months in 8 patients (89%), and within 15 months in 1 patient (11%). Six patients who presented with macroscopic hematuria showed improvement to microscopic hematuria after treatment for 1-2 months, and further improvement to disappearance of microscopic hematuria at 4 to 18 months. Follow-up of the 9 patients showed no residual abnormality at 2 to 4 years. Table 5 summarizes the changes in proteinuria, hematuria and eGFR in these patients.

Discussion

The pathologic lesions encountered in HSPN vary from the most common lesion of segmental proliferation[12] to the rarest membranoproliferative-like lesion (ISKDC grade VI). Only 3.7% of the 245 patients with HSPN

were confirmed by renal biopsy as ISKDC grade VI in our hospital between 2008 and 2010. This rate is slightly different from that reported in other studies (5.7%,[6] 8.6%,[7] 2%,[10] 1.1%[9]). Such differences may be due to lack of strict criteria for the histological diagnosis, time of initial biopsy, selection of cases, and genetic background.

Our study showed that 20.9% of the 245 patients with HSPN presented with NS. This rate is similar to that reported previously by others (23.5% and 17.8%).[9,23] The major clinical manifestation in patients with ISKDC grade VI HSPN in the present study was NS with hematuria, accounting for 78%. Two of the 9 patients with ISKDC grade VI HSPN also showed moderate proteinuria and nephrotic range proteinuria with hematuria. These findings highlight the seriousness of the clinical presentation in ISKDC grade VI HSPN, which is in agreement with previous reports.[8,24,25]

What is the pathogenic mechanism of massive proteinuria in ISKDC grade VI? While this issue was not directly examined in the present study, evidence suggests that such proteinuria is associated with excessive activation and proliferation of mesangial cells, and podocyte lesions. In the present study, microscopic examination showed diffuse mesangial and endocapillary proliferation in all renal biopsies. Proliferative mesangial cells interposed between endothelial cells and glomerular basement membrane (GBM). Chemokines generated by mesangial cells can trigger proliferation of mesangial cells and podocytes through interaction with their receptors, which also regulates inflammatory cell migration and adherence to GBM, with resultant proteinuria.[26,27] Furthermore, Shankland[28] proposed that the diffuse glomerular endocapillary proliferation and nodule formation may result in mechanical traction of the GBM, followed by compensatory podocyte hypertrophy and shedding. The podocyte is the most important and final part of the glomerular filtration barrier.[29] In our study, podocyte hypertrophy, shedding, and cytoplasmic absorption droplets were observed in most specimens, accompanied by diffuse glomerular endocapillary proliferation and nodule formation. Therefore, podocyte lesions in ISKDC grade VI HSPN should be taken into account in any clinicopathological evaluation as well as in any future histopathological classification of HSPN.

A few small cellular crescents were also observed in 6 specimens, but this finding was not a major pathological feature of ISKDC grade VI HSPN; only 4% to 25% of the glomeruli showed this abnormality. Kinoue et al[30] suggested the involvement of glomerular endocapillary proliferation, fibrinoid necrosis and infiltrating inflammatory cells in the process of crescent formation. Crescent formation in a high proportion of glomeruli seems to be a marker of poor prognosis in HSPN, especially when more than 50% glomeruli are affected.[8,9] In our study, prognosis was not influenced by the finding of a few small cellular crescents. In this regard, a recent study found interstitial fibrosis and percentage of sclerotic glomeruli, but not crescents, to be associated with poor prognosis.[31] Only mild degrees of glomerulosclerosis and tubulointerstitial fibrosis were noted in our study, and fewer patients with ISKDC grade VI HSPN showed tubulointerstitial fibrosis compared with those with ISKDC grade IV and V HSPN.

Immunofluorescence examination in the present study identified glomeruli with IgA and fibrinogen deposition in the mesangial area, together with segmental deposition in the capillary tufts. On the other hand, all patients had normal serum complement levels. These two features could be used to differentiate ISKDC grade VI HSPN from idiopathic membranoproliferative glomerulonephritis (MPGN). Three cases showed marked mesangial and capillary tuft deposition of fibrinogen, a finding that could correlate with clotting and thrombosis.

Both full recovery and progression to end-stage renal failure or death have been reported previously for patients with ISKDC grade VI HSPN (Table

Table 6. Summary of previous reports of ISKDC grade VI Henoch-Schönlein purpura nephritis

References	Study design	Subjects	Pathology	Treatment	Follow-up (range)	Outcome (number of patients)
Counahan et al[6]	Retrospective	5	Class VI	None (*n*=2), IS (*n*=2), pred+IS (*n*=1)	≥6.5 y	Normal (2), abnormal (2), death (1)
Lee & Ha[24]	Case report	1	Class VI	Pulse mpred+oral ACEI+CYC	3 mon	Normal
Shenoy et al[31]	Retrospective	3	Class VI (50% cres, *n*=1)	Oral pred+CYC	3.6-13.7 y	Normal (1), abnormal (1), ESKF (1)
Soylemezoglu et al[10]	Retrospective	2	Class VI	No data	No data	Normal (1), abnormal (1)
Kawasaki et al[32]	Retrospective	4	Class VI	Pulse mpred+UK+CYC	2 y	No data
Ohara et al[23]	Case report	1	Class VI (11.5% cres)	Pulse mpred+PP+UK+ tonsillectomy	5 y	Normal

IS: immunosuppressants; pred: prednisolone; mpred: methyl prednisolone; ACEI: angiotensin converting enzyme inhibitors; CYC: cyclophosphamide; PP: plasmapheresis; UK: urokinase; ESKF: end-stage kidney failure; cres: crescent.

6).[6,9,24,25,32,33] In our study, all patients were followed up for 2 to 4 years, and good outcome was noted. This could be related to the early diagnosis following renal biopsy, aggressive therapy, and the presence of only mild glomerulosclerosis and chronic tubulointerstitial lesions at disease onset in 2 of the 9 patients. Our treatment regimen included the combination of ACE inhibitors, pulse methylprednisolone, oral prednisone and immunosuppressants. Previous studies[34,35] indicated that ACE inhibitors ameliorate hyperfiltration-induced proteinuria. Moreover, the use of corticosteroids and immunosuppressants, such as cyclophosphamide[36] and tripterygium glycosides,[37] prevent proteinuria and hematuria through the inhibition of chemokine production.

On the other hand, one study[38] reported the diagnosis of chronic kidney disease (CKD) in 40% HSPN patients with nephrotic syndrome. Taken together, it seems that the early and aggressive treatment employed in our patients prevented the development of CKD, with a risk of progression to CKD at 40%. In this regard, previous pathological studies indicated that renal function impairment correlates with the extent of tubulointerstitial damage rather than with the degree of glomerular damage.[39-41] In our study, all patients had mild tubulointerstitial fibrosis with normal blood pressure at onset of the disease and none had persistent proteinuria. Interestingly, Counahan et al[6] reported that significant changes in prognosis of patients with HSPN occurred more than two years after presentation, with deterioration of clinical and renal function occurring in some patients. These results call for close 5- or 10-year follow-up in such patients.

In summary, the present study demonstrated that the main clinical renal manifestations of ISKDC grade VI HSPN at onset were NS and hematuria, without hypertension or renal failure. The renal prognosis was satisfactory during the short follow-up period, probably due to the mild degree of glomerulosclerosis and tubulointerstitial damage, mild crescent formation, and early and aggressive use of immunosuppressive therapy.

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Ethical approval: This study was approved by the ethics committee of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine (No. 2013HL043-01).

Competing interest: None declared.

Contributors: HYJ proposed the study and wrote the first draft. YXQ analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. HYJ is the guarantor.

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