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CASE BASED REVIEW

Podocytic infolding glomerulopathy: two new cases with connective tissue disease and literature review

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Abstract

Podocytic infolding glomerulopathy (PIG) is a newly proposed disease entity, and only 29 cases have been reported worldwide so far, characterized by microspheres or microtubular structures or both associated with podocytic infolding into the glomerular basement membrane (GBM) on electron microscopy. We present two new cases of PIG with connective tissue disease (CTD), one with primary Sjögren's syndrome and the other with systemic lupus erythematosus (SLE), and make a systemic review of the literature. In the entire 31 patients of PIG, 24 (77.42%) were women and seven (22.58%) were men, with an average age of 41.2 ± 15.2 (ranging from 14 to 79) years old. Almost two-thirds of patients (67.74%) were diagnosed with CTD, in which 76.19% were SLE. All patients presented with proteinuria and six (19.35%) patients were accompanied with hematuria. Serum creatinine was elevated in six (19.35%) patients. Pathological findings of all patients were consistent with PIG characteristics, and four patients with repeated renal biopsies further provided profound insights.

Keywords Podocytic infolding glomerulopathy · Sjögren's syndrome · Systemic lupus erythematosus

Introduction

Podocytic infolding glomerulopathy (PIG) is a newly recognized disease entity in recent years. It was first presented in 1992 when Sato H and his colleagues described three patients with collagen diseases whose renal biopsies appeared to have fine electron-dense deposits in glomerular basement membrane (GBM) [1]. The concept of PIG was then proposed in 2008 by the Japanese Society of Nephrology as they collected 25 cases with glomerulopathy characterized by microspheres or microtubular structures or both associated with podocytic infolding into the GBM on electron microscopy [2]. Thereafter, only four cases with PIG have been reported worldwide in almost 10 years, with two from Japan [3, 4], one from Korea [5], and one from India [6]. Herein, we present two more cases of PIG, one with primary Sjögren's syndrome (pSS) and the other with systemic lupus erythematosus (SLE). Our two cases represent the first identification of PIG in China and increase the total number of PIG cases to 31.

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Case report

Case 1

A 27-year-old female was admitted in July 2017, complaining recurrent pain and swelling of bilateral parotid glands for 5 years, dry mouth and dry eyes for 2 years, nocturia for 1 year, and diarrhea for 10 days. Five years ago, the patient developed intermittent enlargement and tenderness of parotid glands, and she was diagnosed with parotitis in the local hospital. Two

years ago, she experienced dry mouth, dry eyes, and difficulty in swallowing foods without water. Meanwhile, she suffered from polyarthritis as well as Raynaud phenomenon. She then visited our hospital, and laboratory tests demonstrated antinuclear antibody (ANA) 1:160, anti-SSA antibody (+++), anti-SSB antibody (+++), C3 0.80 g/L (reference range, 0.82–1.80 g/L), C4 0.102 g/L (reference range, 0.1–0.4 g/L), rheumatoid factor (RF) 84.6 (< 15) IU/mL, and immunoglobulin G (IgG) 46.6 (7–16) g/L. Urinalysis and serum creatinine were normal. She was diagnosed with pSS and managed with prednisolone and hydroxychloroquine. The symptoms relieved and she spontaneously stopped all medications. One year ago, she developed nocturia, 2–3 times per night without foamy urine or gross hematuria. Twenty-four-hour urine protein was 151 mg/day, and urinary albumin-to-creatinine ratio (ACR) was 110.18 mg/g (reference range, < 25 mg/g) without hematuria. Serum creatinine was 131 μmol/L, potassium 3.1 mmol/L, and chloride 110 mmol/L. Arterial blood gas analysis revealed pH value was 7.348, base excess − 9.0 mmol/L, actual bicarbonate 15.40 mmol/L, and anion gap 9.2 mmol/L. Renal tubular acidosis and chronic kidney disease were considered, and prednisolone 48 mg was administered once daily; hydroxychloroquine and mycophenolate mofetil (MMF) were initiated. But the patient again discontinued all medications half a month before the latest admission. Ten days ago, she developed diarrhea 5–10 times each day with upper abdominal pain which could be relieved after bowel movement. For past medical history, she was otherwise healthy except that she had Hashimoto's thyroiditis. On admission, white blood cell (WBC) was 3.8×10^9/L, hemoglobulin (HGB) 79 g/L, platelet (PLT) 363×10^9/L, IgG 24.80 g/L, serum creatinine 168 μmol/L, ACR 291.18 mg/g, and 24-h urine protein was 629 mg with a urine of pH 6.5. The B ultrasound revealed normal-sized kidneys with enhanced echo in the parenchyma and diminished corticomedullary differentiation. Renal biopsy was performed. Light microscopy showed a total of 19 glomeruli, out of which 10 had global sclerosis and one with segmental sclerosis, and the remaining glomeruli were normal. Generally, the tubulointerstitial lesion affected approximately 75% of the cortex area, with severe vacuole degeneration in renal tubular epithelial cells as well as predominant infiltration of plasma cells and mild fibrosis in the renal interstitium. Immunofluorescent staining of glomeruli was positive for IgM and all were negative for IgG, IgA, C3, C1q, or PLA2R. Immunohistochemical staining of plasma cells infiltrating in the renal interstitium was negative for IgG4. Electron microscopy revealed irregularly thickened GBM and endothelial cell swelling with extensive foot process effacement. Diffuse distribution of microspheres was noticed in the GBM (Fig. 1). The renal pathology was consistent with PIG and chronic interstitial nephritis secondary to pSS. Oral citrate potassium was administered to correct metabolic acidosis and hypokalemia. Prednisolone 48 mg once daily and hydroxychloroquine 0.2 g twice daily were administered. However, the patient had poor compliance and took the medications intermittently. On March 15, 2018, when she was on prednisone 10 mg daily and hydroxychloroquine 0.2 g daily, laboratory tests demonstrated serum creatinine was 292 μmol/L, 24-h urine protein 1327 mg, and ACR 673.91 mg/g. Intravenous methylprednisolone 80 mg daily was administered, which was gradually tapered to 32 mg daily before her discharge on April 8, 2018. One month later, ACR decreased to 90.57 mg/g and serum creatinine to 157 μmol/L. The significance of regular medication adherence was emphasized, but still we lost her follow-up thereafter.

Case 2

A 23-year-old female was admitted into our hospital in May 2018, complaining recurrent abdominal pain and diarrhea for 4 years with foamy urine for 3 months. Four years ago, she developed abdominal pain and diarrhea with fever. The abdominal computed tomography (CT) was normal, and ANA, anti-RNP, and anti-SSA antibodies were positive. SLE was considered and she was managed with glucocorticoids, hydroxychloroquine, and MMF. Three months ago, she developed abdominal pain and diarrhea again with nausea and vomiting, accompanied with pitting edema of bilateral lower extremities and foamy urine. There was no gross hematuria. The serum C3 was 0.51 g/L, C4 0.06 g/L, albumin 23.9 g/L, IgG 4.41 g/L, serum creatinine 47 μmol/L, and erythrocyte sedimentation rate (ESR) 21 mm/h. ANA was 1:40 and anti-ribonucleoprotein antibody was positive, but anti-dsDNA, anti-Sm, and anti-phospholipid antibody were negative. Urinalysis showed red blood cell (+), and 24-h urine protein was 16,796.8 mg. Light microscopy showed a total of 23 glomeruli with thickened GBM. Vacuoles and crater-like structures were visualized in the GBM. The renal interstitium had no infiltration and mild fibrosis. Immunofluorescent staining of glomeruli was positive for IgM and negative for IgG, IgA, C3, C1q, PLA2R, or THSD7A. Electron microscopy revealed irregularly thickened GBM with diffused microspheres and endothelial cell swelling with extensive foot process effacement (Fig. 2). Prednisolone 40 mg daily, hydroxychloroquine 0.2 g twice daily, and tacrolimus 1 mg twice daily were initiated. During the follow-up on November 22, 2018, she was on prednisone 10 mg daily, hydroxychloroquine 0.1 g twice daily, and tacrolimus 1.5 mg twice daily. Her serum creatinine was 64 μmol/L, and urinalysis showed slight proteinuria (±), ACR 333.33 mg/g, and negative hematuria.

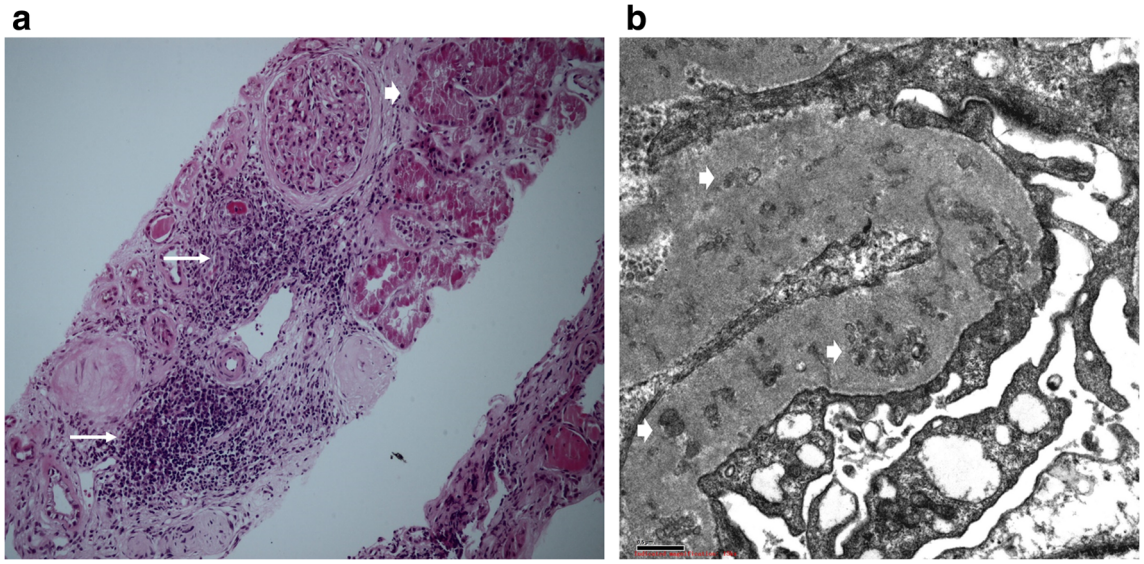

Fig. 1 Renal pathology for case 1 patient. **a** Light microscopic findings of HE staining. The renal tubular epithelial cells had severe vacuole degeneration (arrowhead). The renal interstitium was predominantly infiltrated by plasma cells (arrow) (magnification, ×200). **b** Electronic microscopic findings. Electronic microscopy showed irregularly thickened glomerular basement membrane and endothelial cell swelling with extensive foot process effacement. Diffuse microspheres were found in the glomerular basement membrane (arrowhead) (magnification, ×15,000)

Literature review

We reviewed the literature and analyzed the 29 previously reported cases together with our 2 new cases (Table 1). GraphPad Prism 7 was used for analysis. *t* test/Mann–Whitney *U* test was applied as appropriate. In the entire 31 patients, 16 patients (51.61%) were diagnosed with SLE or lupus-like condition, accompanied with pSS in three patients and Takayasu's disease in one patient. Five patients (16.12%) were diagnosed with other CTDs, including one with mixed connective tissue disease (MCTD), one with undifferentiated connective tissue disease (UCTD), two with pSS, and one with rheumatoid arthritis (RA) with SS. Besides, one patient (3.23%) was diagnosed with chronic thyroiditis, one (3.23%) with vesicoureteral reflux

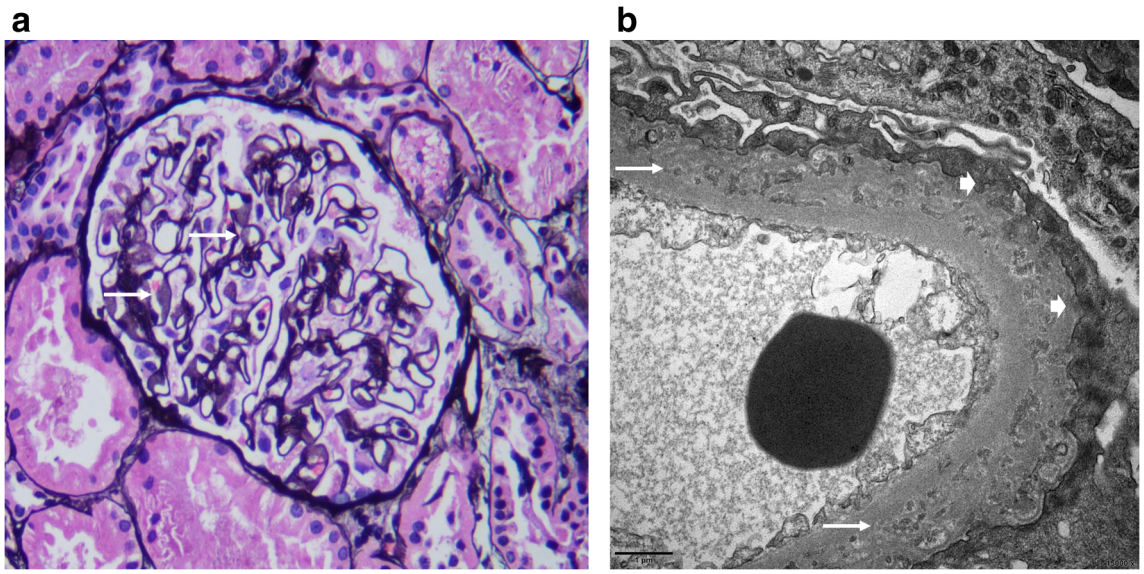

Fig. 2 Renal pathology for case 2 patient. **a** Light microscopic findings of periodic acid-silver methenamine staining. Thickened glomerular basement membrane and vacuole-like structures were visualized (arrow). The renal interstitium had no infiltration and mildly fibrosis (magnification, ×400). **b** Electronic microscopic findings. Electron microscopic findings revealed irregularly thickened glomerular basement membrane and endothelial cell swelling with extensive foot process effacement (arrowhead). Diffuse microspheres were found in the glomerular basement membrane (arrow) (magnification, ×15,000)

Table 1 Clinical characteristics of PIG patients

Case no.	Age(years)	Sex	Country	Concomitant disease	24hUP (g/day)	Hematuria (/HPF)	SCr (mg/dl)	Bp (mmHg)	Treatment
1	31	M	Japan	SLE	0.5	< 1	1.9	154/99	PSL 20 mg/day
2	37	F	Japan	SLE	1	< 1	1.2	124/71	PSL 20 mg/day, MMF
3	40	F	Japan	SLE	1.5	< 1	0.5	104/70	N/A
4	30	F	Japan	SLE	1.6	1 +	0.5	110/72	PSL (pluse×3)
5	61	F	Japan	SLE, Takayasu's arteritis	1.7	< 1	0.9	142/82	PSL 40 mg/day, CsA
6	29	F	Japan	SLE, hydronephrosis due to lupus cystitis	1.6	< 4	0.7	132/78	PSL 20 mg/day
7	46	F	Japan	SLE, hydronephrosis due to lupus cystitis	0.6	< 4	0.5	132/74	PSL 15 mg/day
8	27	F	Japan	SLE	2.7	< 3	0.4	120/70	PSL 30 mg/day, MMF
9	53	M	Japan	SLE, bilateral ureteral stone	3.1	3 +	0.9	150/82	PSL 30 mg/day
10	23	F	Japan	SLE	1.8	3 +	0.5	130/70	PSL 40 mg/day
11	31	F	Japan	SLE	0.5	< 1	0.9	100/60	PSL 20 mg/day
12	24	F	Japan	SLE, Sjogren syndrome	6	< 4	0.6	114/70	PSL (pluse×3)
13	49	M	Japan	PBC, Sjogren syndrome, cystitis, finally SLE	2.2	< 1	1.1	140/90	PSL 40 mg/day
14	20	F	Japan	Lupus-like (3 items)	1.4	< 1	1.4	140/80	NP
15	47	F	Japan	RA, Sjogren syndrome	1.3	< 1	0.6	131/81	N/A
16	51	F	Japan	Sjogren syndrome	3.7	< 1	0.6	120/65	PSL 40 mg/day
17	30	F	Japan	MCTD	0.3	< 1	0.9	110/60	PSL 15 mg/day
18	54	F	Japan	VUR with bilateral hydronephrosis	6	< 1	2.5	160/100	NP
19	57	F	Japan	Hypothyroidism, chronic thyroiditis	0.32	< 1	0.6	101/65	NP
20	45	M	Japan	NP	2.61	< 1	0.7	118/75	PSL 50 mg/day
21	42	F	Japan	Ovarian mature teratoma	7.5	3 +	0.77	120/85	NP
22	69	F	Japan	NP	1.6	< 4	0.9	145/80	NP
23	46	M	Japan	HBVsAg (+)	4	< 1	1.2	130/86	NP
24	59	M	Japan	Neuroendocrine carcinoma of the stomach	0.6	< 1	5.1	140/86	PSL (pluse×3)
25	45	F	Japan	NP	1.5	< 1	0.8	108/80	PSL 30 mg/day
26	14	F	Japan	NP	3.06	< 1	0.45	Normal	PSL 40 mg/day
27	79	M	Japan	Multiple myeloma	1.42	< 1	1.28	140/67	PSL 20 mg/day
28	44	F	Korea	Lupus-like	N/A	N/A	0.45	100/70	PSL 10 mg/day
29	45	F	India	UCTD	5.8	2 +	1.65	130/80	PSL, MMF, RTX
30	27	F	China	Sjogren syndrome	0.63	< 1	1.9	112/54	PSL 40 mg/day, HCQ
31	23	F	China	SLE	16.8	1 +	0.53	118/94	PSL 30 mg/day, FK506, HCQ

PIG, podocytic infolding glomerulopathy; *SLE*, systemic lupus erythematosus; *PBC*, primary biliary cirrhosis; *RA*, rheumatoid arthritis; *MCTD*, mixed connective tissue disease; *UCTD*, undifferentiated connective tissue disease; *VUR*, vesicoureteral reflux; *NP*, not particular; *N/A*, not available; *24hUP*, 24-h urine protein; *HPF*, high power field; *SCr*, serum creatinine; *Bp*, blood pressure; *PSL*, prednisolone; *MMF*, mycophenolate mofetil; *CsA*, cyclosporin A; *RTX*, rituximab; *FK506*, tacrolimus; *HCQ*, hydroxychloroquine

(VUR) and bilateral hydronephrosis, one (3.23%) with HBsAg (+), three (9.68%) with tumors, and four (12.90%) with not particular diagnosis. Twenty-four (77.42%) patients were women and seven (22.58%) were men. Their ages ranged from 14 to 79 years old, with the average age ± standard deviation (SD) being 41.2 ± 15.2 years old. Women were younger than men (38.17 ± 2.89 years old vs. 51.71 ± 5.59 years old) ($P = 0.035$).

All 31 patients presented with proteinuria, ranging from 0.3 g/day to 16.8 g/day, with a median (Q1, Q3) as 1.6 (0.91, 3.25) g/day. In nine patients (29.03%), the urine protein was greater than 3.0 g/day. There was no significant difference between female and male patients ($P = 0.96$) regarding the 24-h urine protein. Six patients (19.36%) also presented with hematuria. Hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) was present in ten patients (32.26%). Serum creatinine levels were elevated (≥ 1.4 mg/dl)

in six patients (19.35%). The median creatinine in females was significantly lower than that in male patients (0.65 (0.5, 0.9) mg/dl vs. 1.2 (0.9, 1.9) mg/dl; $P = 0.018$) (Fig. 3).

All patients had renal biopsy performed, and podocytic infoldings were all identified (Table 2). At the time of PIG diagnosis, the electron microscopy demonstrated that 30 (96.77%) patients had microspheres in the GBM with or without microtubules, and only one (3.23%) patient had microtubules without microspheres. GBM thickening was present in 29 (93.55%) patients and absent in one patient with SLE and one with no particular diagnosis. Dense deposits in GBM were observed in seven (22.58%) patients and absent in 24 (77.42%) patients. All the seven patients with dense deposits in GBM were related with SLE or lupus-like disease, and their renal sections were all positive on immunological staining. In the 24 patients without dense deposits in GBM, nine were negative in immunostaining and 15 were positive. On the other hand, all the nine patients negative in immunostaining did not have dense deposits in GBM. These nine patients were comprised of four with SLE, one with pSS, two with thyroid diseases, one with not particular diagnosis, and one with multiple myeloma.

Four patients had repeated renal biopsies during their disease courses, which provided extremely valuable information to better understand and investigate the pathology of PIG. Two of them had previous renal biopsy in their medical history before the diagnosis of PIG, and the other two repeated their renal biopsy after diagnosis of PIG on follow-ups [3, 7–9]. The former two cases were similar. Both were females in their thirties with the first renal biopsy indicating lupus nephritis class II. They respectively repeated the renal biopsies 3 and 5 years later when the pathology suggested PIG [7, 8]. The third case was a 54-year-old woman who presented with nephrotic syndrome and diagnosed as vesicoureteral reflux (VUR) with bilateral hydronephrosis. Her first renal biopsy demonstrated the presence of focal segmental glomerulosclerosis and diffused podocytic infoldings and numerous spherical microstructures in the GBM. The second biopsy repeated 17 months later revealed remarkably decreased podocytic infoldings and partly degenerated intramembranous microstructures. Neither dense deposits nor immunostaining was positive in either biopsies [9]. The fourth case was a 14-year-old girl with proteinuria whose renal biopsy

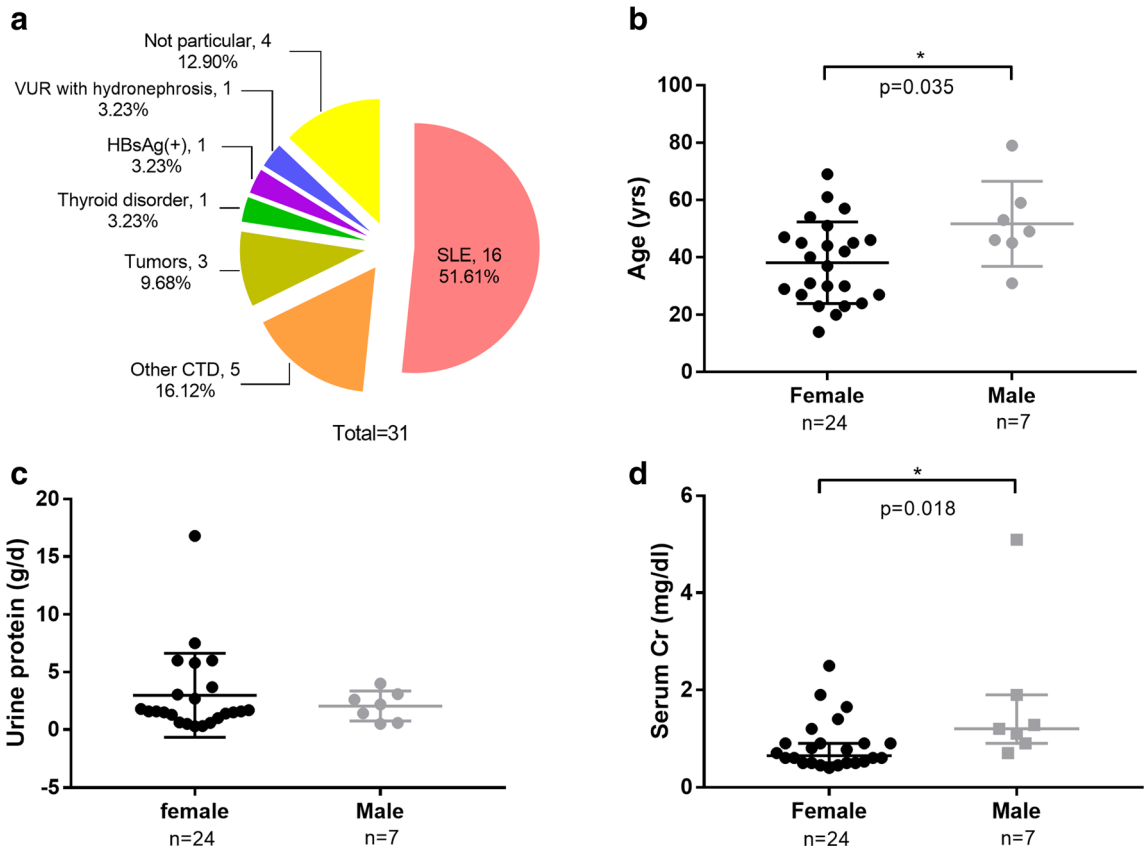

Fig. 3 The concomitant diagnosis of patients with PIG, and the characteristics between female and male patients were compared. **a** The concomitant diseases of PIG, in which SLE comprises 51.61%. **b** Women patients (38.17 ± 2.89 years old) were younger than men (51.71 ± 5.59 years old) ($P = 0.035$). **c** All patients had proteinuria, and there was no significant difference between female and male patients ($P = 0.96$) regarding the 24-h urine protein. **d** Serum creatinine levels were elevated (≥ 1.4 mg/dl) in 6 patients (19.35%). The median (Q1, Q3) creatinine in females (0.65 (0.5, 0.9) mg/dl) was lower than that of male patients (1.2 (0.9, 1.9) mg/dl) ($P = 0.018$)

Table 2 Pathological characteristics of PIG patients

Case no.	Age(years)	Sex	Light microscopy diagnosis	Podocyte infolding	Microsphere	Cluster formation	Microtubule	Dense deposit in GBM	GBM thickening	Staining
1	31	M	LN class I	Present	Present	Absent	Absent	Absent	Present	All negative
2	37	F	LN class II	Present	Present	Absent	Present	Absent	Present	G, A, C3, C1q
3	40	F	LN class II	Present	Present	Absent	Present	Absent	Present	G, A, C3, C1q
4	30	F	LN class II	Present	Present	Absent	Absent	Present	Present	G, A, C3c, C1q, C5b-9
5	61	F	LN class II	Present	Present	Absent	Absent	Absent	Present	G, M, C1q
6	29	F	LN class V	Present	Present (50–100 nm)	Present	Present	Absent	Present	All negative
7	46	F	LN class V	Present	Present	Present	Present	Absent	Present	All negative
8	27	F	LN class V	Present	Present	Present	Present	Present	Present	G, A, M, C3, C1q, C5b-9
9	53	M	LN class V	Present	Present	Absent	Present	Absent	Present	All negative
10	23	F	LN class V	Present	Present	Present	Present	Present	Present	G
11	31	F	LN class V	Present	Present	Absent	Present	Present	Present	G
12	24	F	LN class V	Present	Present	Absent	Present	Present	Present	G, M, C1q
13	49	M	MPGN type 3	Present	Absent	Absent	Present	Absent	Absent	G, A
14	20	F	MGA	Present	Present	Absent	Absent	Absent	Present	G + -
15	47	F	MGA	Present	Present	Absent	Absent	Present	Present	G, A, M
16	51	F	MGA	Weak	Present	Absent	Present	Absent	Present	All negative
17	30	F	MGA	Present	Present	Absent	Absent	Absent	Present	G
18	54	F	FSGS + bubbling	Present	Present	Present	Absent	Absent	Present	All negative
19	57	F	FSGS + bubbling	Weak	Present (6–310 nm)	Absent	Absent	Absent	Present	All negative
20	45	M	FSGS + bubbling	Weak	Present (50–70 nm)	Absent	Present	Absent	Present	G, A, C3
21	42	F	FSGS+MGN	Weak	Present (65–130 nm)	Present	Absent	Absent	Present	G + -
22	69	F	MGN stage 3 > 2	Present	Present	Present	Absent	Absent	Present	G, A, M, C3
23	46	M	MGN stage 3 > 2	Present	Present (40–60 nm)	Present	Present	Absent	Present	G + -, anti HBVs Ag
24	59	M	MGN stage 3 > 2	Present	Present	Absent	Absent	Absent	Present	M
25	45	F	MGN stage 3 > 2	Present	Present (50–150 nm)	Present	Present	Absent	Present	G, A, C3
26	14	F	MGA → FSGS	Present	Present	Absent	N/A	Absent	Absent	All negative
27	79	M	Chronic renal ischemia?	Present	Present	N/A	N/A	Absent	Present	All negative
28	44	F	MGA? MN stage III?	Present	Present (80–120 nm)	N/A	Present	Few	Present	M
29	45	F	MN stage II-III	Present	Present	Present	N/A	Absent	Present	G, C3
30	27	F	Chronic interstitial nephritis	Present	Present	Absent	Absent	Absent	Present	M
31	23	F	MGN + bubbling	Present	Present	Absent	Absent	Absent	Present	M

PIG, podocytic infolding glomerulopathy; *LN*, lupus nephritis; *GBM*, glomerular basement membrane; *N/A*, not available; *MN*, membranous nephropathy; *MPGN*, membranoproliferative glomerulonephritis; *MGA*, minor glomerular abnormality; *FSGS*, focal segmental glomerulosclerosis; *MGN*, membranous glomerulonephritis; *G*, IgG; *A*, IgA; *M*, IgM

indicated minor glomerular abnormality (MGA) and microspheres in the GBM. Not particular diagnosis other than PIG was made. Three years later, the second biopsy revealed focal segmental glomerulosclerosis (FSGS) with a lesser degree of podocytic infoldings than those of the first biopsy. Immunofluorescent staining was negative at the beginning, but in the second biopsy, it turned positive for IgM, C3, and C1q in the segmental sclerosis lesions [3].

For the treatment, 25 patients were treated with prednisolone, ranging from 10 to 50 mg daily, with three patients who also received pulse therapy. In five patients with SLE,

additional immunosuppressants including MMF, cyclosporine A, hydroxychloroquine, and tacrolimus were administered. In the patient with UCTD, MMF and a single dose of rituximab were applied aside from glucocorticoids. During follow-ups in 28 patients, urine protein declined in 26 patients, but remained similar or even deteriorated in two patients.

Discussion

So far, 31 cases have been identified with PIG. All patients reported were from Asia, mostly from Japan. Whether it also occurs in Caucasian or other ethnics remains unknown. Almost two-thirds of patients (67.74%) were diagnosed with CTD, in which 76.19% were SLE. The remaining underlying diseases include tumors in three cases, and chronic thyroiditis and hydronephrosis as well as hepatitis B virus infection in one case. There are four cases who did not have particular concomitant diseases at the time of diagnosis with PIG. It was unclear whether these four cases should actually represent "primary" PIG.

The microspheres or microtubules characterized in PIG have been proved to be originated mostly from the podocytes rather than the endothelial or mesangial cells in series renal sections, but the mechanisms of podocytic cytoplasmic infolding or budding into the GBM are not clear. It has been suggested that complement activation in situ on the microstructures may play a role [10]. However, in some cases, the immunostainings were negative for immunoglobulin or complement. Besides, two patients with SLE also had hydronephrosis due to lupus cystitis. The possible role of mechanical factors in the pathogenesis of PIG is unneglectable and needs further evaluation.

Because the diagnosis of PIG exclusively depends on the morphological manifestations of electron microscopy, it has been doubted whether it should be considered as an independent disease entity or it may only represent some variants of known glomerulopathies. Since the light microscopic findings of PIG resemble those of membranous nephropathy (MN), Masuda Y et al. reviewed 126 renal biopsies of primary MN to address the differences between these two groups [10]. Results demonstrated that 98 cases (77.8%) had occasional invagination of podocytes (large cytoplasmic projections from podocytes) in the GBM, and 40 cases (31.7%) had additional spherical microparticles including podocyte infolding (microspheres and microtubules connected with podocytes), cell debris, and virus-like particle types. Only one case displayed numerous microspheres that were probably caused by infolding of podocytes. They concluded that while podocyte invagination was common in primary MN, diffused podocyte infoldings should be considered as a new pathology entity. This study also emphasized the importance of excluding cell debris and virus-like particles before making conclusion of PIG when there were microstructures in the GBM [10]. More stringent and detailed criteria regarding the pathological manifestations of PIG should be further investigated.

Besides, four cases with repeated renal biopsy mentioned above brought forth inspiring insights into the nature of PIG. Two cases suggested that ordinary lupus nephritis could progress into combination with PIG in certain stage of the disease, while another two cases indicated that typical manifestations of PIG might disappear or even fade away as time lapsing. It is difficult to figure out whether the reduction of PIG characteristic microstructures in the latter two cases is due to the improvement of disease after treatment or represents the late stage of PIG as it evolves. However, in the fourth case, the MGA progressed to FSGS according to the light microscopy while the microstructures in the GBM unparallelly decreased [3]. So, the decrease in microstructures does not seem to be like the result of disease alleviation. More serial biopsies can better depict the transformational features of PIG, but the invasiveness of renal biopsy may largely limit its application.

To summarize, PIG is a newly proposed disease entity with undetermined etiology and unknown pathogenesis. It deserves more attention and further investigation to promote the awareness of this disease. More practical and detailed diagnostic criteria and serial renal biopsies reported by experienced pathologists are warranted.

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Compliance with ethical standards

Disclosures None.

Ethics The case report was approved by the Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University, School of Medicine, and informed consents were obtained in both patients.

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