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Membranous nephropathy after multiple Hymenoptera stings: a case report

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Abstract

An association between Hymenoptera (bee and wasp) stings and nephrotic syndrome has been rarely reported. We report a case of nephrotic syndrome after multiple Hymenoptera stings, and membranous nephropathy was later diagnosed by a kidney biopsy. The patient was a 79-year-old woman who was stung by Hymenoptera at seven sites on her body. A weight gain of 3.7 kg was observed in the patient at 1 week after being stung, and she had considerable edema in both lower extremities. A urine protein concentration of 14.8 g/g creatinine and a serum albumin concentration of 1.7 g/dL led to the diagnosis of nephrotic syndrome. A percutaneous kidney biopsy 8 days after the Hymenoptera stings showed stage I membranous nephropathy. She was in complete remission 1 week after the administration of oral prednisolone 40 mg/day, which was started 14 days after Hymenoptera stings, and had no relapse of nephrotic syndrome. To the best of our knowledge, this is the first report of biopsy-proven membranous nephropathy caused by Hymenoptera stings.

Keywords: Hymenoptera sting, membranous nephropathy, nephrotic syndrome

Introduction

Hymenoptera (bee or wasp) stings lead to local reactions characterized by redness and swelling at the stinging site and systemic allergic reactions or anaphylaxis [1]. There are various other unusual reactions to Hymenoptera stings, such as hemolysis, rhabdomyolysis, acute renal failure, and nephrotic syndrome [2,3]. Minimal change nephrotic syndrome [4–8], proliferative glomerulonephropathy [9], mesangial proliferative glomerulonephritis [10], and mesangial proliferative glomerulonephropathy with possible early membranous nephropathy [11] have been reported as nephrotic syndrome caused by Hymenoptera stings. However, the reports providing histological results of nephrotic syndrome caused by Hymenoptera stings are limited. In this report, we present a case of stage I membranous nephropathy induced by Hymenoptera stings in which complete remission was achieved by oral prednisolone.

Case report

A 79-year-old Japanese woman was stung by Hymenoptera at seven sites on her body, with one on her right arm and six on her left arm, while working in the garden. On the same day, a dermatologist prescribed an anti-histamine, but the patient experienced mild edema in both lower extremities in the evening. Her symptoms did not improve after

taking the anti-histamine. Subsequently, a physician noted hypoalbuminemia and proteinuria (3+) on day 7 after she was stung by Hymenoptera. On the same day, she was referred to our hospital with the suspicion of nephrotic syndrome.

The patient's past medical history was notable for dyslipidemia, insomnia, gastroesophageal reflux disease, and allergic bronchitis. She was taking pravastatin 5 mg/day, zolpidem 10 mg/day, esomeprazole 10 mg/day, tranexamic acid 750 mg/day, carbocysteine 1500 mg/day, and rebamipide 300 mg/day for these conditions. Eight years before the current hospital admission, she was diagnosed with non-tuberculous mycobacteriosis and was followed up with no medication.

On admission, a physical examination showed no localized swelling at the sting sites, but strong edema was observed in both lower extremities, and her blood pressure was 137/74 mmHg. She weighed 52.7 kg, which indicated a weight gain of 3.7 kg for 7 days. Her laboratory data on admission are shown in Table 1. A urinalysis showed 4+ proteinuria (14.18 g/g creatinine [Cr]). Quantitative protein excretion on admission was 7.16 g/day. Urinary sediment showed 1–4 red blood cells/high power field, and 1–4 granular casts/whole field. A laboratory investigation showed that the blood urea nitrogen concentration was 10 mg/dL, serum creatinine concentration was 0.54 mg/dL, total protein concentration was 4.9 g/dL, albumin concentration was 1.7 g/dL, total cholesterol

concentration was 401 mg/dL, low-density lipoprotein cholesterol concentration was 266 mg/dL, and selectivity index of urinary protein was 0.11. The clinical data of proteinuria ≥ 3.5 g/day and serum albumin concentration ≤ 3.0 g/dL led to a diagnosis of nephrotic syndrome.

An ultrasound-guided percutaneous kidney biopsy was performed on the second day of hospitalization. Light microscopy showed minor glomerular abnormalities with moderate atherosclerotic lesions in the arterioles and small arteries, and slight tubulointerstitial changes. Neither spikes nor a bubbly appearance of the capillary wall of glomeruli was observed (Fig. 1). An immunofluorescence examination using fresh frozen sections showed moderate, irregular and segmental staining for immunoglobulin (Ig) G (Fig. 2a), IgM (Fig. 2b), C3c (Fig. 2c), and fibrinogen (Fig. 2d) on the glomerular capillary loops. Staining of M-type phospholipase A_2 receptor (PLA_2R) on paraffin sections was negative in the glomerular capillary loops, although autofluorescence from red blood cells was positive for segmental staining (Fig. 2e, 2f). On electron microscopy, there were diffuse and partially segmental podocyte foot process effacement with microvillous formation and segmental irregular subepithelial electron-dense deposits in glomeruli without apparent formation of spikes, consistent with stage I membranous nephropathy (Fig. 3). Laser microdissection and mass

spectrometry (LC-MS/MS) [12] in this case did not show the presence of PLA_2R, thrombospondin type-1 domain-containing 7A (THSD7A) [13], nerve epidermal growth factor-like 1 (NELL-1) [14], exostosin 1/exostosin 2 (EXT1/EXT2) [15], semaphorin 3B (SEMA3B) [16], protocadherin 7 (PCDH7) [17], and neural cell adhesion molecule 1 (NCAM1) [18] (data not shown). Serum PLA_2R antibody was negative at 24 days after steroid treatment. Secondary causes of membranous nephropathy were investigated. Serology was negative for hepatitis B and C, and a serological test for syphilis and the *Treponema pallidum* hemagglutination test were both negative. Angiotensin-converting enzyme, anti-nuclear antibodies, antibody to Sjögren's syndrome A and B, and anti-U1 RNP antibody were normal. Carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 125, α-fetoprotein, and soluble interleukin-2 receptor concentrations were normal, and did not indicate malignancy. A stool occult blood test was negative. Esophagogastroduodenoscopy also showed no evidence of malignancy. Computed tomography scans of the chest showed lobular central granular shadows, and enlarged bronchioles and nodules in both lung fields, consistent with non-tuberculous mycobacteriosis. An abdominal computed tomography scan showed a small amount of ascites, with no renal enlargement or atrophy. We diagnosed membranous nephropathy secondary to Hymenoptera stings on the basis of

the renal biopsy findings, clinical and laboratory data, and exclusion of other causes of membranous nephropathy.

On the seventh day of hospitalization (14 days after Hymenoptera stings), prednisolone was started at an oral dose of 40 mg/day (0.8 mg/kg body weight), and the dose was decreased every 2 weeks. The clinical course of the patient is shown in Fig. 4. On the 13th day of hospitalization, urinalysis revealed no proteinuria (0.00 g/gCr). She had complete remission (6 days after steroid treatment) and no relapse of nephrotic syndrome. Laboratory data 6 months after steroid therapy were as follows: urinary protein, 0.00 g/gCr; no abnormalities in urinary sediment; serum total protein concentration, 6.3 g/dL; serum albumin concentration, 4.0 g/dL; serum creatinine concentration, 0.48 mg/dL; estimated glomerular filtration rate, 91 mL/min/1.73 m^2; total cholesterol concentration, 155 mg/dL, and low-density lipoprotein-cholesterol concentration, 68 mg/dL.

Discussion

Since the first report on nephrotic syndrome due to Hymenoptera (wasp or bee) stings by Rytand in 1955 [3], approximately 20 related case reports have been published. A renal biopsy was performed in nine patients with nephrotic syndrome due to

Hymenoptera. Table 2 shows clinical features, pathology of kidney, treatment and outcome of these 9 patients. Six patients were diagnosed with minimal change nephrotic syndrome (MCNS) [4–8]. One patient had proliferative glomerulonephropathy [9], one had mesangial proliferative glomerulonephritis [10], and one had mesangial proliferative glomerulonephropathy with possible early membranous nephropathy [11]. Although the majority case (4/6) with MCNS after Hymenoptera stings resulted in complete remission with steroid treatment [5–8], cases with proliferative glomerulonephritis did not resolve promptly [9–11]. The outcome of 2 MCNS cases was unknown [4]. A case with proliferative glomerulonephritis resulted in chronic dialysis [9], a case with membranous proliferative glomerulonephritis relapsed twice [10], and another case with mesangial proliferative glomerulonephritis resulted in incomplete remission [11]. To the best of our knowledge, this is the first case report of definite membranous nephropathy with nephrotic syndrome after multiple Hymenoptera stings resulted in complete remission with steroid therapy.

IgG4-dominance had the highest specificity in the differentiation of membranous nephropathy, just as high as that for anti-PLA_2R seropositivity [19]. Staining for IgG subclasses from the renal biopsy was not performed in this case because of missing fresh frozen tissue. M-type PLA_2R on glomerular podocytes has been identified as a major

antigen in idiopathic membranous nephropathy [20]. PLA_2 is associated with diverse physiological processes, such as toxicity (neurotoxicitiy and myotoxicity), pathology (inflammation and cancer), and physiology (proliferation, contraction, and secretion) [21]. Bee venom contains PLA_2, which is a major allergen, and the peptide melittin and hyaluronidase, whereas wasp venom contains antigen 5, different phospholipases, and hyaluronidase [1]. PLA_2 accounts for up to 12% of bee venom contents [22]. It is reported that there was a strong direct correlation between anti-PLA_2R and anti-secreted PLA_2 antibodies [23]. PLA_2 injected by Hymenoptera stings may have contributed to the development of membranous nephropathy in the current case. However, serum PLA_2R antibody after steroid treatment in this case was negative. In addition, immunofluorescence using paraffin section for PLA_2R antigen and LC-MS/MS findings of renal biopsy specimen could not be detected in this case (Fig. 2e). We cannot conclude that there was a relationship between PLA_2, which is contained in Hymenoptera venom, and the antigen of this patient's membranous nephropathy. However, we could not rule out the possibility that treatment with steroid stabilized the proteinuria, and circulating anti-PLA_2R concentrations became undetectable, as previously reported [24]. Segmental and irregular deposition of IgG and electron-dense deposits in stage I membranous nephropathy were observed, but PLA_2R was not detected by LC-MS/MS and

immunofluorescence using paraffin-embedded sections. However, one possibility is still remained that the reduced sensitivity of antigen detection in paraffin-embedded sections and the low levels of antigen in segmental deposition of immune complexes, which may fall below the sensitivity of detection of LC-MS/MS, may have contributed to the failure to detect PLA_2R in this study. The reason for the different renal pathological findings in nephrotic syndrome after Hymenoptera (wasp or bee) stings is unclear, but may be related to toxic envenomation between bees and wasps and between a few stings and thousands of stings [8]. Further case reports are necessary to determine the cause and reason for different renal pathological findings in nephrotic syndrome after Hymenoptera stings.

The onset of this case was rapid (edema was observed on the same day, and hypoalbuminemia and urinary protein were observed on day 7 after the Hymenoptera stings), and the reaction against steroid therapy was also rapid. These clinical courses were different from general membranous nephropathy. A rapid onset of edema and nephrotic syndrome, but not a rapid response against steroid therapy, may be characteristics of nephropathy after Hymenoptera stings. In previous studies, the timing of edema was 2 days to 2 weeks [5,7–11], and the timing of nephrotic syndrome was several days to 4 weeks [5,7–11] after Hymenoptera stings. The rapid reaction against steroid therapy has not been reported in previous cases of nephropathy after Hymenoptera

stings [5–8]. The prognosis of nephrotic syndrome with segmental membranous glomerulopathy is favorable; 50% of patients achieve complete remission and 21% achieve partial remission [25]. We consider that the rapid response to steroid therapy in our patient may be related to segmental deposition of IgG on the capillary walls of glomeruli.

The requirement of performing hemodialysis, despite corticosteroid treatment, has been reported in some cases of nephrotic syndrome after Hymenoptera stings [8,9]. This case highlights the importance of an early renal biopsy and early steroid therapy in managing nephrotic syndrome after Hymenoptera stings.

Compliance with Ethical Standards

Funding: None.

Conflict of interest: The authors have declared that no conflict of interest exists.

Consent for publication: Informed consent was obtained from the patient.

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Figure legends

Fig. 1 Light microscopy of a renal biopsy. (a) Moderate atherosclerotic lesions can be seen (periodic acid–Schiff stain, × 200). (b) A normocellular glomerulus with patent capillaries without thickening of glomerular capillary walls can be seen (periodic acid–Schiff stain, ×1000). (c) The apparent spikes or stippling of glomerular basement membranes cannot be seen in glomerulus (periodic acid–silver methenamine–hematoxylin and eosin stain, ×1000).

Fig. 2 Immunofluorescence shows moderate staining for IgG (a), and staining for IgM (b), C3c (c), and fibrinogen (d). Immunofluorescence using paraffin sections for phospholipase A_2 receptor (PLA_2R) (e, f: high magnification of the area indicated by the arrow in e) is negative on the glomerular capillary loops, although autofluorascence from red blood cells was detected.

Fig. 3 Electron microscopy shows the diffuse and partially segmental effacement of the foot processes of podocytes with microvillous formation and irregular segmental subepithelial electron-dense deposits (arrowheads) in glomeruli without apparent spike formation (a,c: ×1500; b,d: ×7000).

Fig. 4 Clinical course of the patient

PSL, prednisolone; Cr, creatinine; U-protein, urinary protein; Alb, serum albumin

Fig1

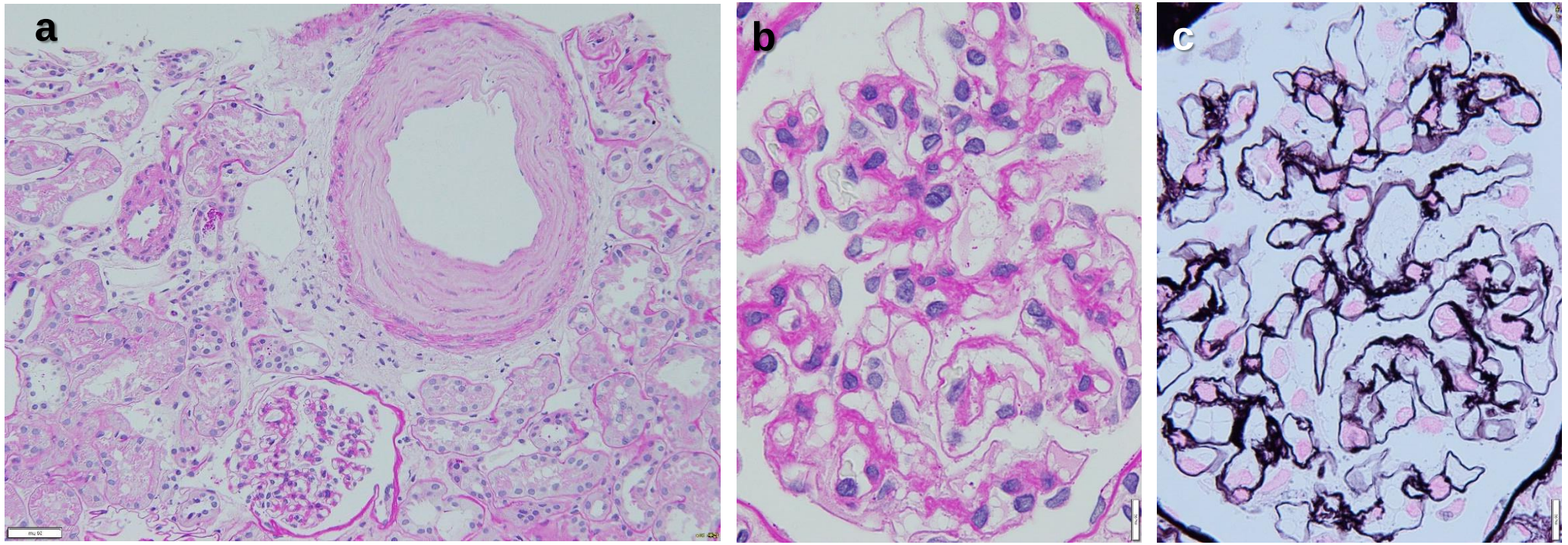

Fig2

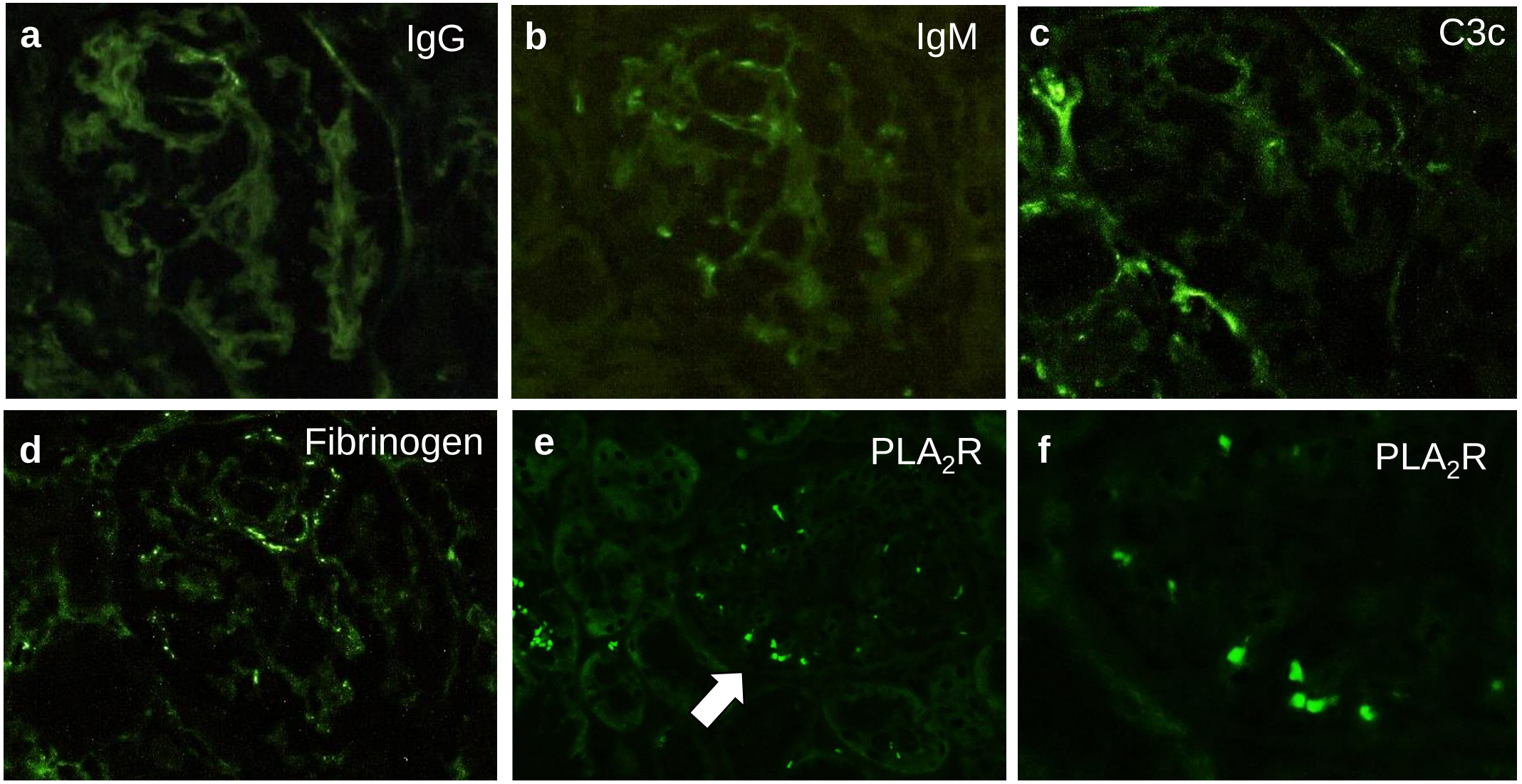

Fig3

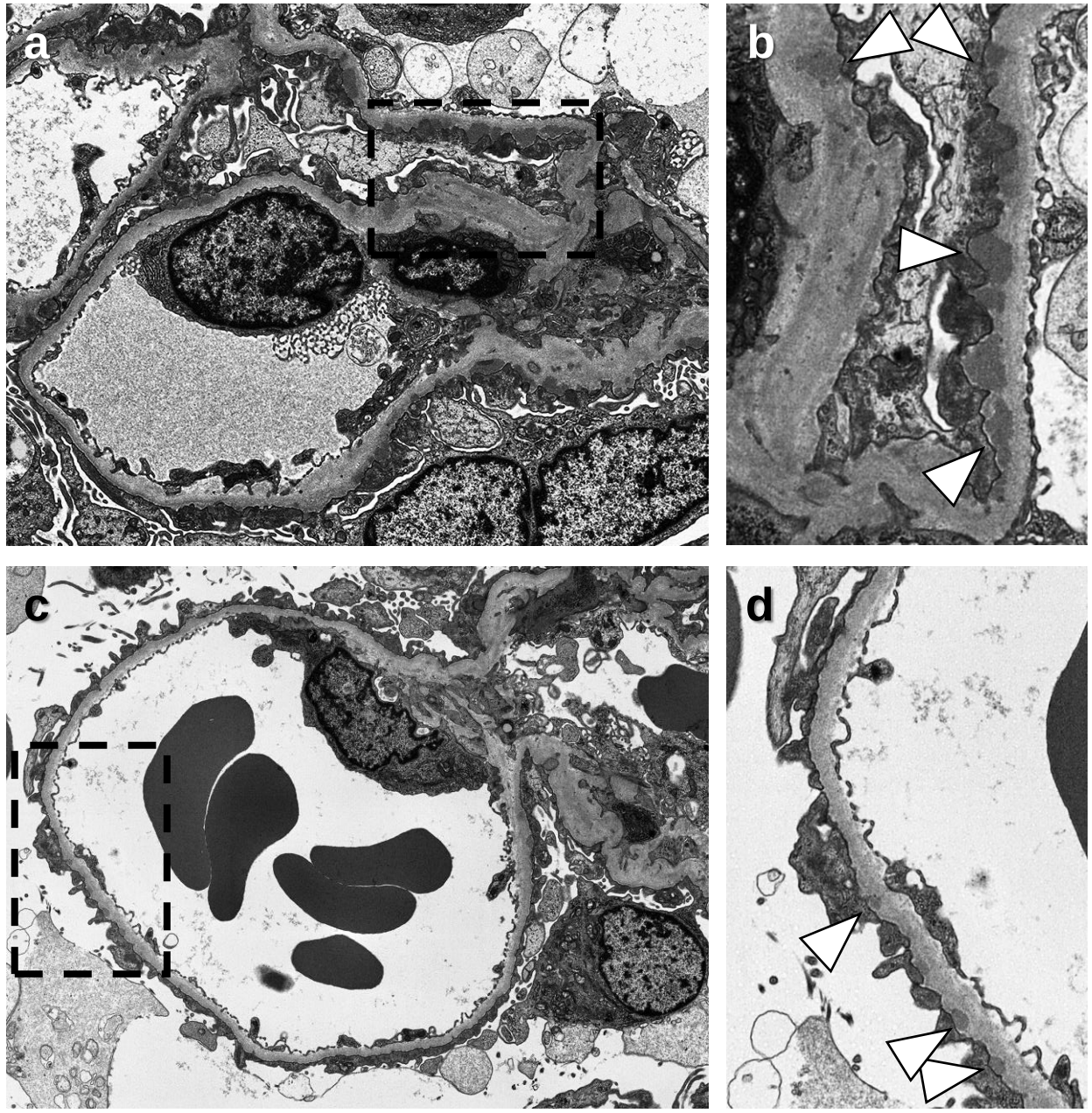

Fig4

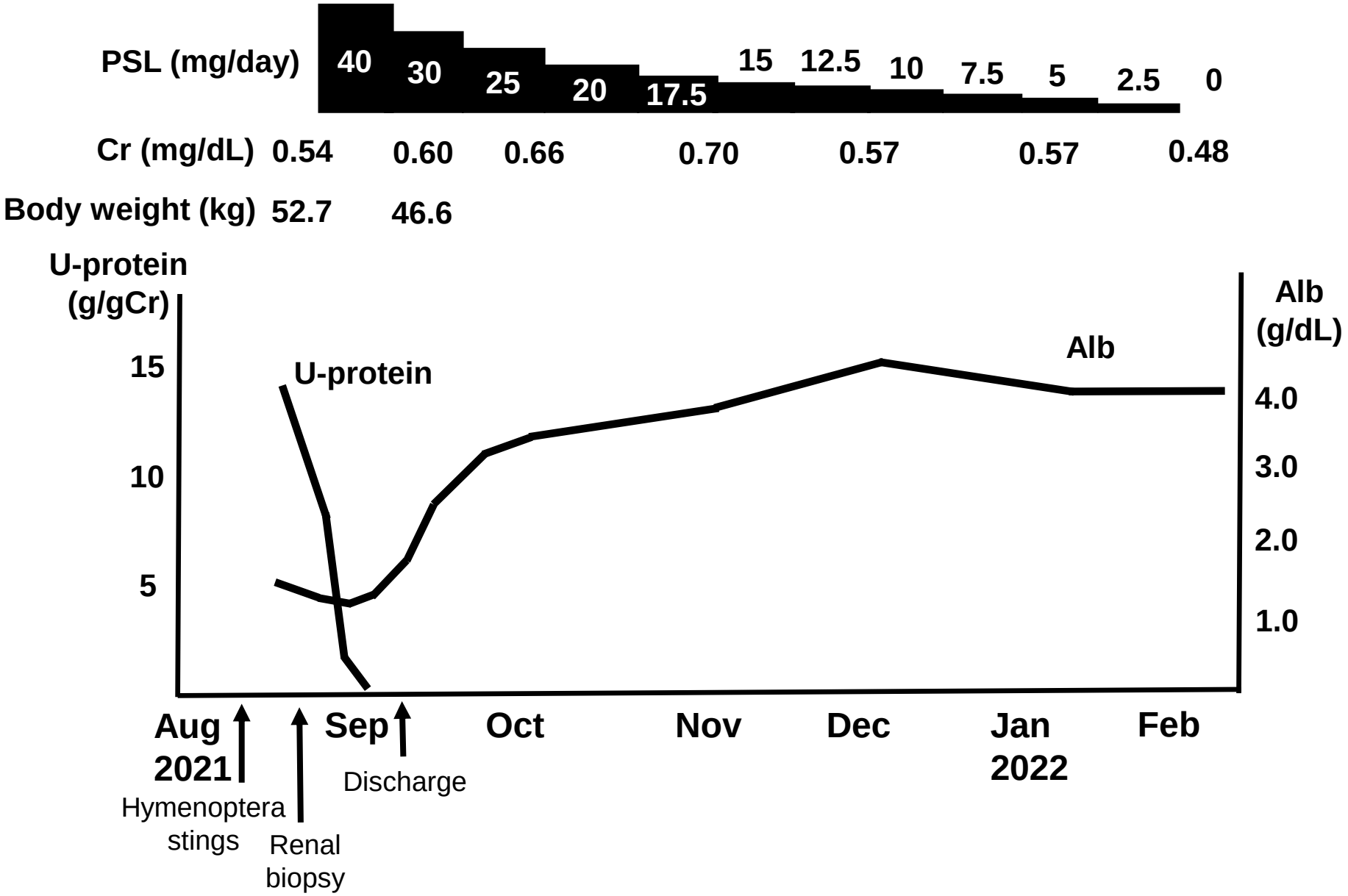
PSL (mg/day)
40
30
25
20
17.5
15
12.5
10
7.5
5
2.5
0
Cr (mg/dL)
0.54
0.60
0.66
0.70
0.57
0.57
0.48
Body weight (kg)
52.7
46.6
U-protein (g/gCr)
15
10
5
U-protein
Alb
Alb (g/dL)
4.0
3.0
2.0
1.0
Aug 2021
Sep
Oct
Nov
Dec
Jan 2022
Feb
Hymenoptera stings
Renal biopsy
Discharge

Table1

Table 1 Laboratory data on admission

Urinalysis		***Peripheral blood***	
Protein	14.18 g/gCr	WBCs	7800 /mm^3
Occult blood	+-	Neut	75.7%
Urine sediment		Lymp	17.4%
RBCs	1-4 /HPF	Mono	3.5%
WBCs	0-1 /HPF	Eosino	2.6%
Granular cast	1-4 /WF	Baso	0.8%
Hyaline cast	1-4/WF	RBCs	4.57 x 10^6 /mm^3
β2-MG	402 μg/L	Hb	13.9 g/dL
		Hct	42.5%
Proteinuria selectivity index	0.11	Plt	30.0 x 10^4 /mm^3
Blood chemistry		***Immunological studies***	
TP	4.9 g/dL	IgG	1128 mg/dL
Alb	1.7 g/dL	IgA	231 mg/dL
TC	401 mg/dL	IgM	92 mg/dL
LDL-C	266 mg/dL	C3	266 mg/dL
HDL-C	107 mg/dL	C4	107 mg/dL
TGs	186 mg/dL	CH50	186 mg/dL
BUN	10 mg/dL	ANA	-
Cr	0.54 mg/dL	HBsAg	-
Na	137 mEq/L	HCVAb	-
K	4.7 mEq/L	Fraction of serum protein	
Cl	106 mEq/L	Alb	44.8%
Ca	10.8 mg/dL	α1-glb	3.6%
P	3.1 mg/dL	α2-glb	21.1%
eGFR	80 mL/min/1.73 m^2	β-glb	12.7%
CRP	0.13 mg/dL	γ-glb	17.8%
FBG	97 mg/dL		

RBCs, red blood cells; WBCs, white blood cells; HPF, high-power field; WF, whole field; β2-MG, β2-microglobulin; TP, total protein; Alb, albumin; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TGs, triglycerides; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, albumin-adjusted calcium; P, phosphorus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; FBG, fasting blood glucose; Neut, neutrophils; Lymp, lymphocytes; Mono, monocytes; Eosino, eosinophils; Baso, basophils; Hb, hemoglobin; Hct, hematocrit; Plt, platelets; Ig, immunoglobulin; C, complement; CH50, 50% hemolytic unit of complement; ANA, anti-nuclear antibody; HBsAg, hepatitis B virus s antigen; HCVAb, hepatitis C virus antibody; glb, globulin.

Table2

Table 2 Clinical features, pathology of kidney, treatment and outcome of patients with nephrotic syndrome after Hymenoptera stings

Author [reference]	Year	Age (y) / sex	Proteinuria (g/day)	Creatinine (mg/dL)	Pathological findings				Treatment	Outcome
					Diagnosis	LM	IF	EM		
Venters et al. [4]	1961	N.A.	N.A.	N.A.	MCNS (2 cases)	Normal	N.A.	FPE	Cortisone	N.A.
Olivero et al. [5]	1981	22 / F	18	N.A.	MCNS	Normal	All negative	FPE No EDD	PSL	CR
Sensirivatana et al. [10]	1984	5 / M	N.A.	Normal	MPG	Mesangial proliferation	IgM, mesangial area	N.A.	PSL	Relapsed twice
Taber et al. [9]	1986	63 / F	3-4	7.1	PGN	Chronic rejection*	All negative	Proliferating glomerular epithelial cells	Prednisone, HD to PD	Chronic dialysis
Revai et al. [6]	1999	16 / F	49 g/L	N.A.	MCNS	Normal	IgM and C1q, mesangial area	N.A.	mPSL + PSL + CPA + CB	CR
Tauk et al. [11]	1999	28 / M	14	0.7	MPGN Possible early MN	Mesangial increase	IgG, IgM, C3, and C4: mesangial area IgG: capillary loops	FPE Subepithelial deposits	PSL + CPA	ICR
Zaman et al. [7]	2001	21 / M	11.5	0.8	MCNS	Normal	All negative	FPE No EDD	PSL	CR
Humeda et al. [8]	2022	67 / M	10.7	3.5	MCNS	Normal	All negative	FPE No EDD	PSL HD for 3 weeks	CR

LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; N.A., not applicable; F, female; M, male; MCNS, minimal change nephrotic syndrome; MPG, mesangial proliferative glomerulonephritis; PGN, proliferative glomerulonephritis; MPGN, mesangial proliferative glomerulonephritis; MN, membranous nephritis; FPE; foot process effacement; EDD, electron-dense deposits; CR, complete remission; ICR, incomplete remission; PSL, prednisolone; mPSL, methyl prednisolone; CB, chlorambucil; CPA, cyclophosphamide; HD, hemodialysis; PD, peritoneal dialysis.

* Vascular sclerosis, chronic changes in renal tubules, patchy interstitial inflammatory infiltrate, and segmental sclerosis of glomerular mesangium.