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3 **Membranous nephropathy after multiple Hymenoptera stings: a case**
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6 **report**
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1
2
3 **Abstract**
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6 An association between Hymenoptera (bee and wasp) stings and nephrotic
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9 syndrome has been rarely reported. We report a case of nephrotic syndrome after multiple
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12 Hymenoptera stings, and membranous nephropathy was later diagnosed by a kidney
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15 biopsy. The patient was a 79-year-old woman who was stung by Hymenoptera at seven
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18 sites on her body. A weight gain of 3.7 kg was observed in the patient at 1 week after
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21 being stung, and she had considerable edema in both lower extremities. A urine protein
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24 concentration of 14.8 g/g creatinine and a serum albumin concentration of 1.7 g/dL led to
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27 the diagnosis of nephrotic syndrome. A percutaneous kidney biopsy 8 days after the
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30 Hymenoptera stings showed stage I membranous nephropathy. She was in complete
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33 remission 1 week after the administration of oral prednisolone 40 mg/day, which was
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36 started 14 days after Hymenoptera stings, and had no relapse of nephrotic syndrome. To
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39 the best of our knowledge, this is the first report of biopsy-proven membranous
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44 nephropathy caused by Hymenoptera stings.
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51 **Keywords:** Hymenoptera sting, membranous nephropathy, nephrotic syndrome
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3 **Introduction**
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6 Hymenoptera (bee or wasp) stings lead to local reactions characterized by
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9 redness and swelling at the stinging site and systemic allergic reactions or anaphylaxis
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12 [1]. There are various other unusual reactions to Hymenoptera stings, such as hemolysis,
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15 rhabdomyolysis, acute renal failure, and nephrotic syndrome [2,3]. Minimal change
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18 nephrotic syndrome [4–8], proliferative glomerulonephropathy [9], mesangial
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21 proliferative glomerulonephritis [10], and mesangial proliferative glomerulonephropathy
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24 with possible early membranous nephropathy [11] have been reported as nephrotic
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27 syndrome caused by Hymenoptera stings. However, the reports providing histological
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30 results of nephrotic syndrome caused by Hymenoptera stings are limited. In this report,
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33 we present a case of stage I membranous nephropathy induced by Hymenoptera stings in
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36 which complete remission was achieved by oral prednisolone.
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45 **Case report**
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47 A 79-year-old Japanese woman was stung by Hymenoptera at seven sites on her
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50 body, with one on her right arm and six on her left arm, while working in the garden. On
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53 the same day, a dermatologist prescribed an anti-histamine, but the patient experienced
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56 mild edema in both lower extremities in the evening. Her symptoms did not improve after
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3 taking the anti-histamine. Subsequently, a physician noted hypoalbuminemia and
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6 proteinuria (3+) on day 7 after she was stung by Hymenoptera. On the same day, she was
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9 referred to our hospital with the suspicion of nephrotic syndrome.
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12 The patient's past medical history was notable for dyslipidemia, insomnia,
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14 gastroesophageal reflux disease, and allergic bronchitis. She was taking pravastatin 5
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16 mg/day, zolpidem 10 mg/day, esomeprazole 10 mg/day, tranexamic acid 750 mg/day,
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19 carbocysteine 1500 mg/day, and rebamipide 300 mg/day for these conditions. Eight years
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22 before the current hospital admission, she was diagnosed with non-tuberculous
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25 mycobacteriosis and was followed up with no medication.
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32 On admission, a physical examination showed no localized swelling at the sting
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34 sites, but strong edema was observed in both lower extremities, and her blood pressure
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36 was 137/74 mmHg. She weighed 52.7 kg, which indicated a weight gain of 3.7 kg for 7
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38 days. Her laboratory data on admission are shown in Table 1. A urinalysis showed 4+
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41 proteinuria (14.18 g/g creatinine [Cr]). Quantitative protein excretion on admission was
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44 7.16 g/day. Urinary sediment showed 1–4 red blood cells/high power field, and 1–4
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47 granular casts/whole field. A laboratory investigation showed that the blood urea nitrogen
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50 concentration was 10 mg/dL, serum creatinine concentration was 0.54 mg/dL, total
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53 protein concentration was 4.9 g/dL, albumin concentration was 1.7 g/dL, total cholesterol
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3 concentration was 401 mg/dL, low-density lipoprotein cholesterol concentration was 266
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6 mg/dL, and selectivity index of urinary protein was 0.11. The clinical data of proteinuria
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9 ≥ 3.5 g/day and serum albumin concentration ≤ 3.0 g/dL led to a diagnosis of nephrotic
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12 syndrome.
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16 An ultrasound-guided percutaneous kidney biopsy was performed on the
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19 second day of hospitalization. Light microscopy showed minor glomerular
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22 abnormalities with moderate atherosclerotic lesions in the arterioles and small arteries,
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25 and slight tubulointerstitial changes. Neither spikes nor a bubbly appearance of the
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28 capillary wall of glomeruli was observed (Fig. 1). An immunofluorescence examination
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31 using fresh frozen sections showed moderate, irregular and segmental staining for
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34 immunoglobulin (Ig) G (Fig. 2a), IgM (Fig. 2b), C3c (Fig. 2c), and fibrinogen (Fig. 2d)
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37 on the glomerular capillary loops. Staining of M-type phospholipase A₂ receptor
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40 (PLA₂R) on paraffin sections was negative in the glomerular capillary loops, although
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43 autofluorescence from red blood cells was positive for segmental staining (Fig. 2e, 2f).
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46 On electron microscopy, there were diffuse and partially segmental podocyte foot
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49 process effacement with microvillous formation and segmental irregular subepithelial
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52 electron-dense deposits in glomeruli without apparent formation of spikes, consistent
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55 with stage I membranous nephropathy (Fig. 3). Laser microdissection and mass
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3 spectrometry (LC-MS/MS) [12] in this case did not show the presence of PLA₂R,
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6 thrombospondin type-1 domain-containing 7A (THSD7A) [13], nerve epidermal growth
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9 factor-like 1 (NELL-1) [14], exostosin 1/exostosin 2 (EXT1/EXT2) [15], semaphorin
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12 3B (SEMA3B) [16], protocadherin 7 (PCDH7) [17], and neural cell adhesion molecule
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15 1 (NCAM1) [18] (data not shown). Serum PLA₂R antibody was negative at 24 days
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17
18 after steroid treatment. Secondary causes of membranous nephropathy were
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21 investigated. Serology was negative for hepatitis B and C, and a serological test for
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24 syphilis and the *Treponema pallidum* hemagglutination test were both negative.
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28 Angiotensin-converting enzyme, anti-nuclear antibodies, antibody to Sjögren's
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31 syndrome A and B, and anti-U1 RNP antibody were normal. Carcinoembryonic antigen,
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34 carbohydrate antigen 19-9, carbohydrate antigen 125, α -fetoprotein, and soluble
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37 interleukin-2 receptor concentrations were normal, and did not indicate malignancy. A
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40 stool occult blood test was negative. Esophagogastroduodenoscopy also showed no
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43 evidence of malignancy. Computed tomography scans of the chest showed lobular
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46 central granular shadows, and enlarged bronchioles and nodules in both lung fields,
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49 consistent with non-tuberculous mycobacteriosis. An abdominal computed tomography
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52 scan showed a small amount of ascites, with no renal enlargement or atrophy. We
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57 diagnosed membranous nephropathy secondary to Hymenoptera stings on the basis of
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3 the renal biopsy findings, clinical and laboratory data, and exclusion of other causes of
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6 membranous nephropathy.
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9 On the seventh day of hospitalization (14 days after Hymenoptera stings),
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11 prednisolone was started at an oral dose of 40 mg/day (0.8 mg/kg body weight), and the
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13 dose was decreased every 2 weeks. The clinical course of the patient is shown in Fig. 4.
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17 On the 13th day of hospitalization, urinalysis revealed no proteinuria (0.00 g/gCr). She
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19 had complete remission (6 days after steroid treatment) and no relapse of nephrotic
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21 syndrome. Laboratory data 6 months after steroid therapy were as follows: urinary protein,
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23 0.00 g/gCr; no abnormalities in urinary sediment; serum total protein concentration, 6.3
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25 g/dL; serum albumin concentration, 4.0 g/dL; serum creatinine concentration, 0.48
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27 mg/dL; estimated glomerular filtration rate, 91 mL/min/1.73 m²; total cholesterol
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29 concentration, 155 mg/dL, and low-density lipoprotein-cholesterol concentration, 68
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31 mg/dL.
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48 **Discussion**

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50 Since the first report on nephrotic syndrome due to Hymenoptera (wasp or bee)
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52 stings by Rytand in 1955 [3], approximately 20 related case reports have been published.
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55 A renal biopsy was performed in nine patients with nephrotic syndrome due to
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3 Hymenoptera. Table 2 shows clinical features, pathology of kidney, treatment and
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6 outcome of these 9 patients. Six patients were diagnosed with minimal change nephrotic
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9 syndrome (MCNS) [4–8]. One patient had proliferative glomerulonephropathy [9], one
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12 had mesangial proliferative glomerulonephritis [10], and one had mesangial proliferative
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15 glomerulonephropathy with possible early membranous nephropathy [11]. Although the
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18 majority case (4/6) with MCNS after Hymenoptera stings resulted in complete remission
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21 with steroid treatment [5–8], cases with proliferative glomerulonephritis did not resolve
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24 promptly [9–11]. The outcome of 2 MCNS cases was unknown [4]. A case with
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27 proliferative glomerulonephritis resulted in chronic dialysis [9], a case with membranous
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30 proliferative glomerulonephritis relapsed twice [10], and another case with mesangial
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33 proliferative glomerulonephritis resulted in incomplete remission [11]. To the best of our
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36 knowledge, this is the first case report of definite membranous nephropathy with
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39 nephrotic syndrome after multiple Hymenoptera stings resulted in complete remission
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42 with steroid therapy.
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48 IgG4-dominance had the highest specificity in the differentiation of membranous
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51 nephropathy, just as high as that for anti-PLA₂R seropositivity [19]. Staining for IgG
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54 subclasses from the renal biopsy was not performed in this case because of missing fresh
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57 frozen tissue. M-type PLA₂R on glomerular podocytes has been identified as a major
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3 antigen in idiopathic membranous nephropathy [20]. PLA₂ is associated with diverse
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6 physiological processes, such as toxicity (neurotoxicity and myotoxicity), pathology
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9 (inflammation and cancer), and physiology (proliferation, contraction, and secretion) [21].
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12 Bee venom contains PLA₂, which is a major allergen, and the peptide melittin and
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15 hyaluronidase, whereas wasp venom contains antigen 5, different phospholipases, and
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18 hyaluronidase [1]. PLA₂ accounts for up to 12% of bee venom contents [22]. It is reported
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21 that there was a strong direct correlation between anti-PLA₂R and anti-secreted PLA₂
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24 antibodies [23]. PLA₂ injected by Hymenoptera stings may have contributed to the
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27 development of membranous nephropathy in the current case. However, serum PLA₂R
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30 antibody after steroid treatment in this case was negative. In addition,
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32
33 immunofluorescence using paraffin section for PLA₂R antigen and LC-MS/MS findings
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36 of renal biopsy specimen could not be detected in this case (Fig. 2e). We cannot conclude
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39 that there was a relationship between PLA₂, which is contained in Hymenoptera venom,
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42 and the antigen of this patient's membranous nephropathy. However, we could not rule
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45 out the possibility that treatment with steroid stabilized the proteinuria, and circulating
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48 anti-PLA₂R concentrations became undetectable, as previously reported [24]. Segmental
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51 and irregular deposition of IgG and electron-dense deposits in stage I membranous
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54 nephropathy were observed, but PLA₂R was not detected by LC-MS/MS and
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3 immunofluorescence using paraffin-embedded sections. However, one possibility is still
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6 remained that the reduced sensitivity of antigen detection in paraffin-embedded sections
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9 and the low levels of antigen in segmental deposition of immune complexes, which may
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12 fall below the sensitivity of detection of LC-MS/MS, may have contributed to the failure
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15 to detect PLA₂R in this study. The reason for the different renal pathological findings in
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18 nephrotic syndrome after Hymenoptera (wasp or bee) stings is unclear, but may be related
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21 to toxic envenomation between bees and wasps and between a few stings and thousands
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24 of stings [8]. Further case reports are necessary to determine the cause and reason for
25
26
27 different renal pathological findings in nephrotic syndrome after Hymenoptera stings.
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32 The onset of this case was rapid (edema was observed on the same day, and
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35 hypoalbuminemia and urinary protein were observed on day 7 after the Hymenoptera
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38 stings), and the reaction against steroid therapy was also rapid. These clinical courses
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40
41 were different from general membranous nephropathy. A rapid onset of edema and
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43
44 nephrotic syndrome, but not a rapid response against steroid therapy, may be
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46
47 characteristics of nephropathy after Hymenoptera stings. In previous studies, the timing
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50 of edema was 2 days to 2 weeks [5,7–11], and the timing of nephrotic syndrome was
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53 several days to 4 weeks [5,7–11] after Hymenoptera stings. The rapid reaction against
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56 steroid therapy has not been reported in previous cases of nephropathy after Hymenoptera
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3 stings [5–8]. The prognosis of nephrotic syndrome with segmental membranous
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6 glomerulopathy is favorable; 50% of patients achieve complete remission and 21%
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9 achieve partial remission [25]. We consider that the rapid response to steroid therapy in
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12 our patient may be related to segmental deposition of IgG on the capillary walls of
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16 glomeruli.
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19 The requirement of performing hemodialysis, despite corticosteroid treatment,
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22 has been reported in some cases of nephrotic syndrome after Hymenoptera stings [8,9].
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25 This case highlights the importance of an early renal biopsy and early steroid therapy in
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28 managing nephrotic syndrome after Hymenoptera stings.
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38 **Compliance with Ethical Standards**

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41 Funding: None.
42

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48 Consent for publication: Informed consent was obtained from the patient.
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3 **Figure legends**
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6 **Fig. 1** Light microscopy of a renal biopsy. (a) Moderate atherosclerotic lesions can be
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seen (periodic acid–Schiff stain, $\times 200$). (b) A normocellular glomerulus with patent
capillaries without thickening of glomerular capillary walls can be seen (periodic acid–
Schiff stain, $\times 1000$). (c) The apparent spikes or stippling of glomerular basement
membranes cannot be seen in glomerulus (periodic acid–silver methenamine–
hematoxylin and eosin stain, $\times 1000$).

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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 A₂ receptor (PLA₂R) (e, f: high magnification of the area indicated by the
arrow in e) is negative on the glomerular capillary loops, although autofluorescence from
red blood cells was detected.

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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: $\times 1500$; b,d: $\times 7000$).

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Fig. 4 Clinical course of the patient

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

Fig1

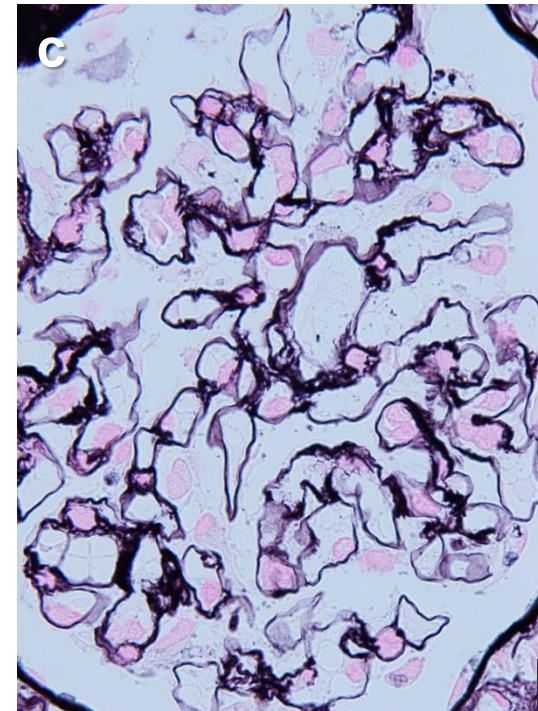
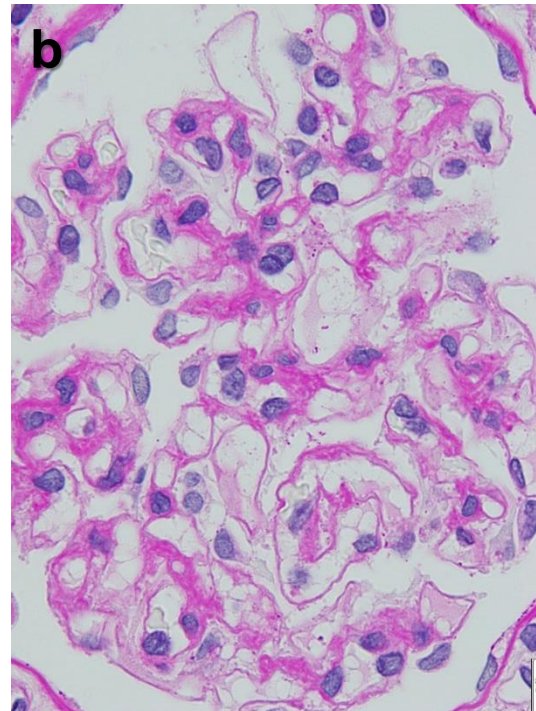
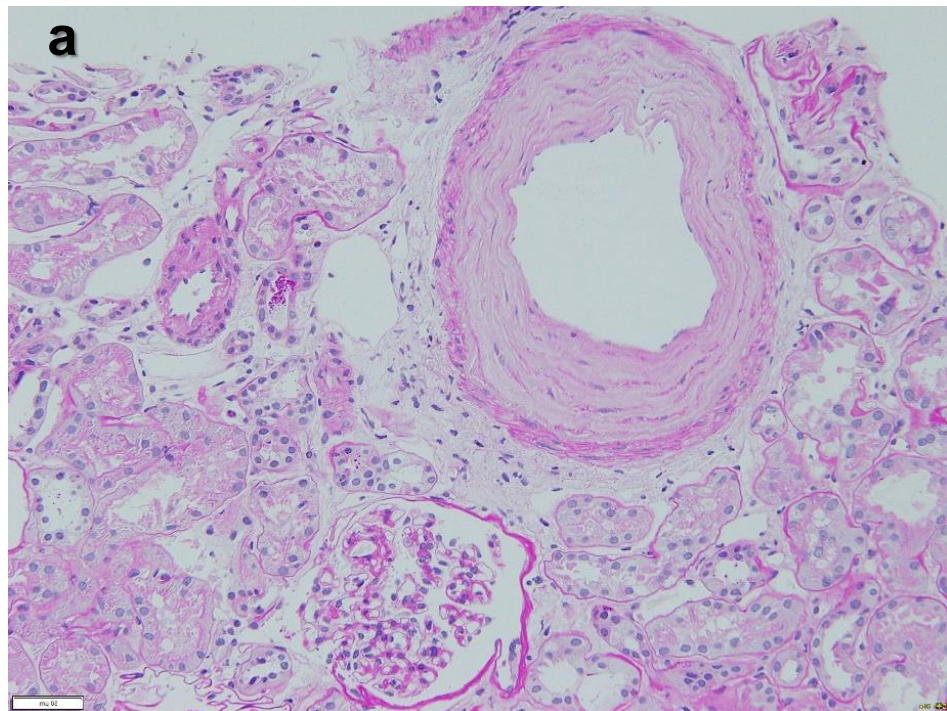


Fig2

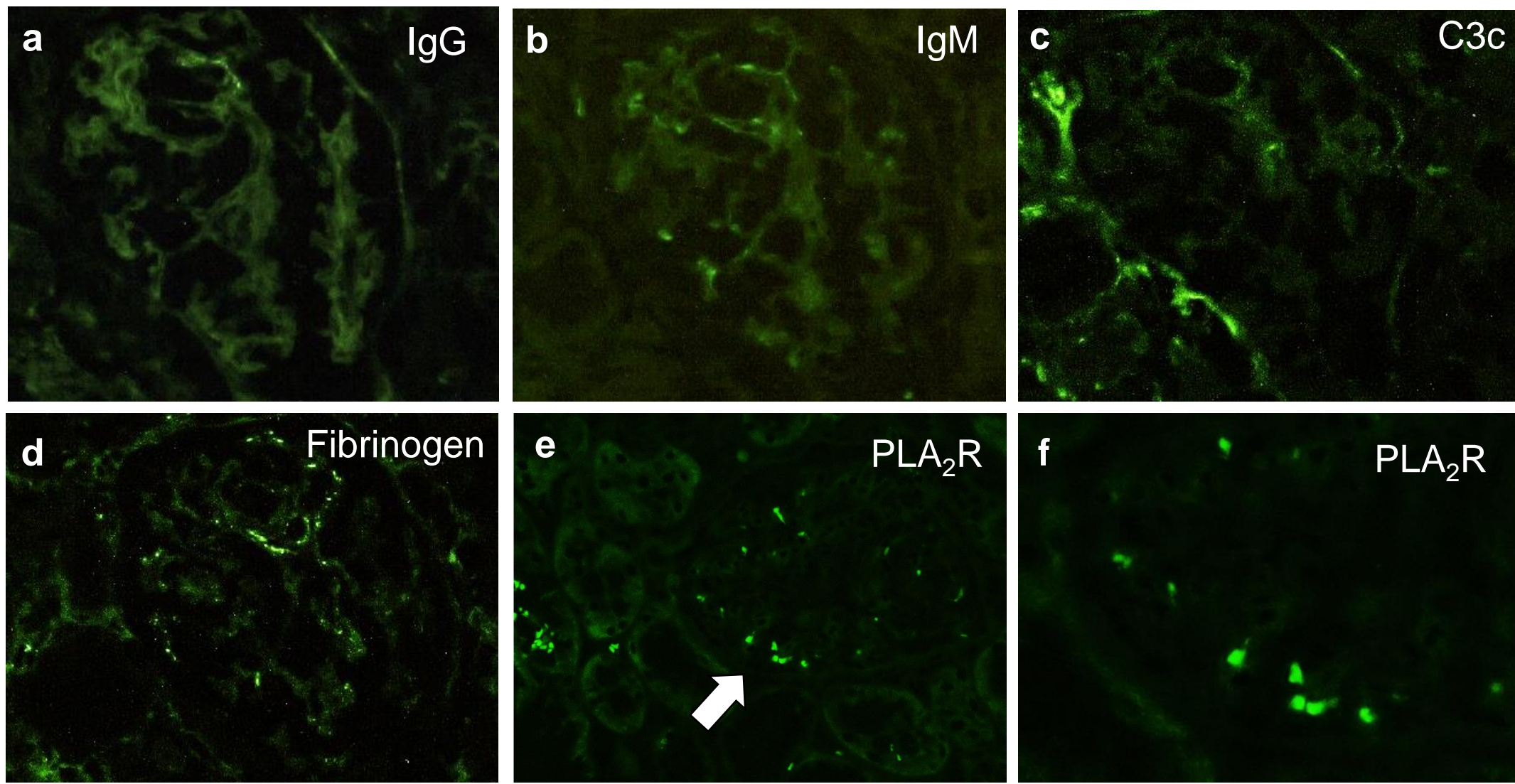


Fig3

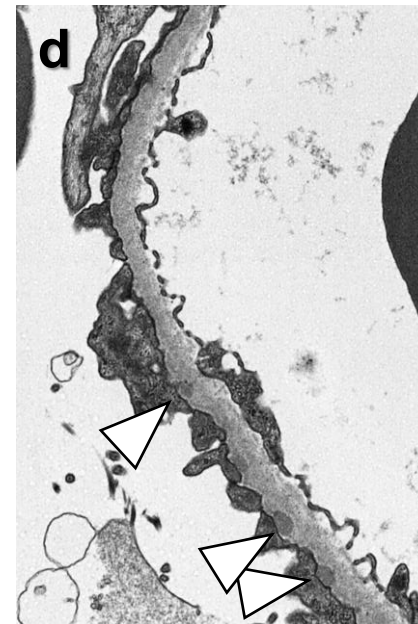
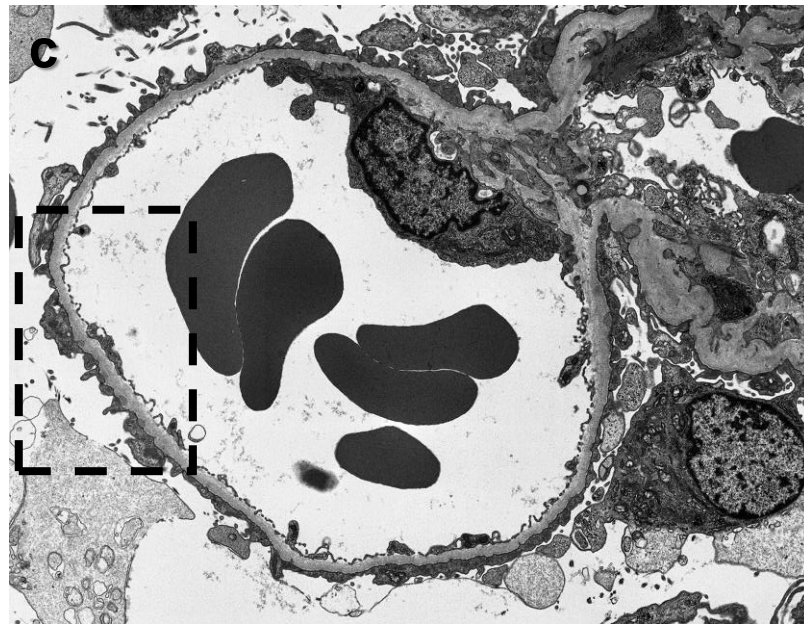
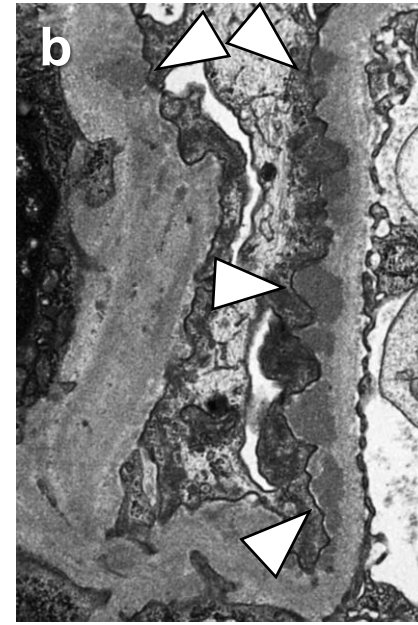
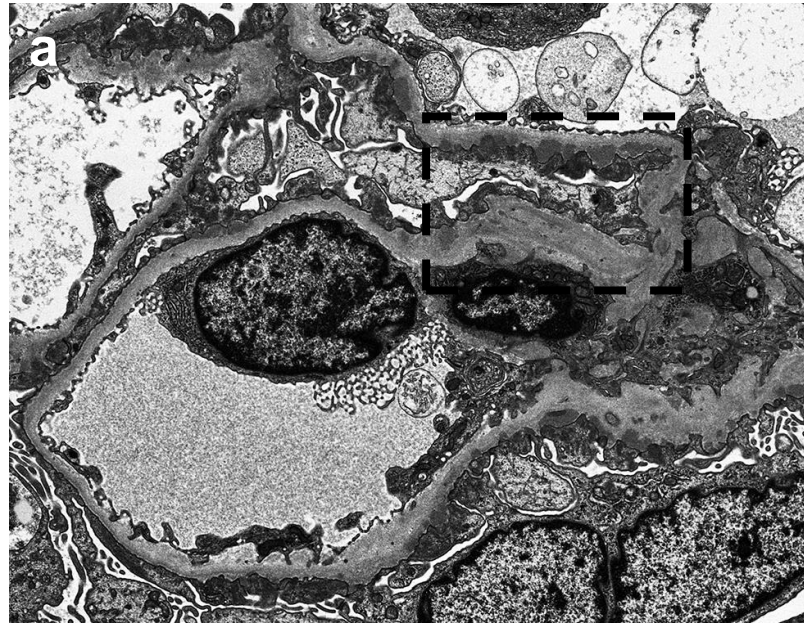


Fig4

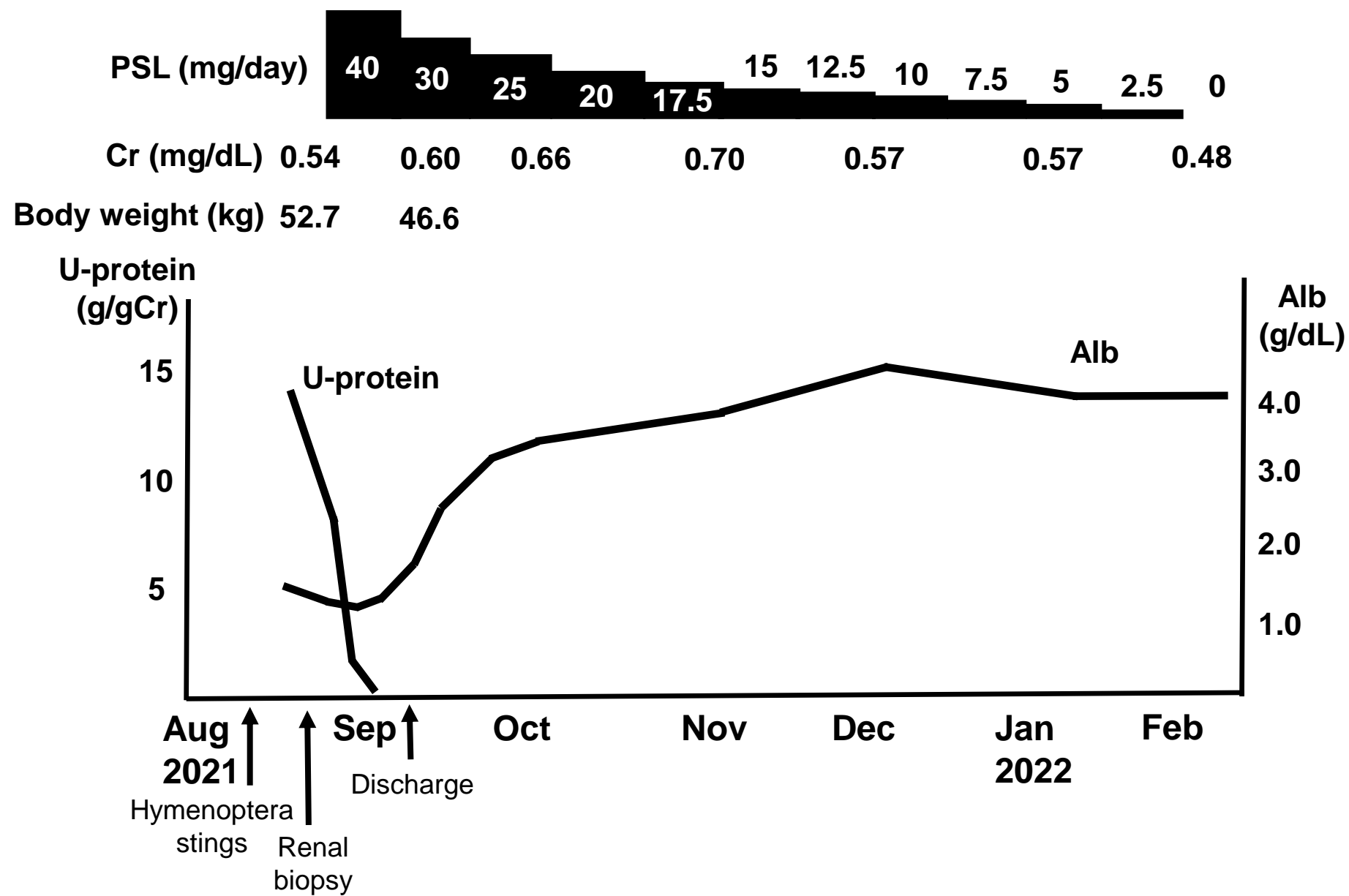


Table 1 Laboratory data on admission

<i>Urinalysis</i>		<i>Peripheral blood</i>	
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%
<i>Proteinuria selectivity index</i>	0.11	Plt	30.0 x 10 ⁴ /mm ³
<i>Blood chemistry</i>		<i>Immunological studies</i>	
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.

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.