Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2020;10:42–50

DOI: 10.1159/000507426
Published online: April 22, 2020

Case Report

Acute Kidney Injury Associated with Minimal Change Nephrotic Syndrome in an Elderly Patient Successfully Treated with both Fluid Management and Specific Therapy Based on Kidney Biopsy Findings

Yuko Oyama[a] Yoichi Iwafuchi[a] Tetsuo Morioka[b] Ichiei Narita[c]

[a]Department of Internal Medicine, Koseiren Sanjo General Hospital, Sanjo, Japan;
[b]Department of Internal Medicine, Kidney Center, Shinrakuen Hospital, Niigata, Japan;
[c]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Keywords

Acute kidney injury · Nephrosarca hypothesis · Elderly patient · Minimal change nephrotic syndrome · Kidney biopsy

Abstract

Oliguric acute kidney injury (AKI) with minimal change nephrotic syndrome (MCNS) has long been recognized. Several mechanisms such as hypovolemia due to hypoalbuminemia and the nephrosarca hypothesis have been proposed. However, the precise mechanism by which MCNS causes AKI has not been fully elucidated. Herein, we describe an elderly patient with AKI caused by MCNS who fully recovered after aggressive volume withdrawal by hemodialysis and administration of a glucocorticoid. A 75-year-old woman presented with diarrhea and oliguria,

KARGER

Yuko Oyama, MD, PhD
Department of Internal Medicine, Koseiren Sanjo General Hospital
5-1-62, Tsukanome
Sanjo 955-0055 (Japan)
oyamayuko@outlook.jp

and laboratory examination revealed nephrotic syndrome (NS) and severe azotemia. Fluid administration had no effect on renal dysfunction, and hemodialysis was initiated. Her renal function improved upon aggressive fluid removal through hemodialysis. Renal pathological findings revealed minimal change disease with faint mesangial deposits of IgA. After administration of methylprednisolone pulse therapy followed by oral prednisolone, she achieved complete remission from NS. The clinical course of this case supports the nephrosarca hypothesis regarding the mechanism of AKI caused by MCNS. Furthermore, appropriate fluid management and kidney biopsy are also important in elderly patients with AKI caused by NS.

Introduction

Minimal change nephrotic syndrome (MCNS) complicated by oliguric acute kidney injury (AKI) has long been recognized [1]. However, its pathophysiological mechanisms have not been fully elucidated. Hypovolemia caused by low plasma oncotic pressure arising from hypoalbuminemia was believed to be the main mechanism, as the depletion of plasma volume with subsequent activation of the renin-angiotensin system was reported to stimulate tubular sodium absorption [2]. However, the observation of volume preservation, or even expansion [3], without renin-angiotensin system activation [4] in patients with nephrotic syndrome (NS) has led to the development of an alternative hypothesis, namely the nephrosarca hypothesis, which involves oliguric AKI in MCNS to reduced glomerular filtration caused by interstitial edema [5].

Assessment of the mechanism underlying AKI is important for prompt therapy and prevention of complications, such as hypovolemic shock or thromboembolism, from excessive diuretic use, or pulmonary edema following albumin infusion. However, as the clinical features of AKI are diverse among patients and disease stages, it is challenging to determine its mechanism in clinical practice. Herein, we report the case of an elderly patient with AKI caused by MCNS who fully recovered after aggressive volume withdrawal by hemodialysis, followed by administration of a glucocorticoid.

Case Report

A 75-year-old woman was admitted to our hospital with a 1-week history of appetite loss, diarrhea, dyspnea, and oliguria. She had a medical history of hypertension and bronchial asthma for 9 years. Both were well controlled with antihypertensive agents (irbesartan and amlodipine combination) and an anti-asthmatic drug (inhalation of a combination drug containing vilanterol trifenatate and fluticasone furoate), respectively. Her renal function was previously unremarkable. Upon admission, her blood pressure was 137/63 mm Hg, her pulse rate was 81 beats/min, and her temperature was 35.8°C. She was 131.3 cm tall and weighed 58.9 kg. She was neither pale nor icteric. A physical examination of the chest and abdomen revealed unremarkable findings, and no lymphadenopathy or skin lesions were observed. She had generalized edema.

Laboratory data upon admission are shown in Table 1. Proteinuria (9.38 g/gCr), hypoalbuminemia (serum albumin, 2.4 g/dL), and renal dysfunction (blood urea nitrogen, 182.0 mg/dL; creatinine [Cr], 7.70 mg/dL) were noted, while anti-neutrophil cytoplasmic antibodies were negative. The serum brain natriuretic peptide (BNP) level was 88.5 pg/mL. Chest radiography revealed slight right pleural effusion, and electrocardiography revealed an incomplete right bundle branch block. Abdominal computed tomography showed slight enlargement of both kidneys. These findings led to the diagnosis of AKI and NS.

Despite infusion of a hypotonic electrolyte solution and discontinuation of the antihypertensive medication (which contained irbesartan, an angiotensin II receptor blocker), diuresis was not accomplished, and her serum Cr level rose to 8.25 mg/dL. On admission day 2, urinary protein excretion was 3–20 g/gCr, which was within the nephrotic range, and hemodialysis was initiated.

On admission day 10, a kidney biopsy was performed to investigate the etiology of AKI and NS. Her serum Cr level was 4.38 mg/dL at that time. Light microscopy of the biopsied sample showed 18 glomeruli, of which 2 were obsolescent. The glomeruli showed minor abnormalities, including very mild segmental mesangial expansion (Fig. 1a). Interstitial edema and tubular necrosis were not observed. Moderate arterial hyalinosis was observed. Immunofluorescence analysis revealed faint and segmental mesangial deposits of IgA, IgG, and C3 (Fig. 1b). Electron microscopy revealed diffuse effacement of podocyte foot processes, with microvillus transformation. Electron-dense deposits were seen in the paramesangial areas, and they were less frequent and of lower density than those observed in typical IgA nephropathy (Fig. 1c). On the basis of these pathological findings, a diagnosis of MCNS associated with faint mesangial IgA deposits was made.

Oliguria continued for approximately 2 weeks, and cardiomegaly and anasarca deteriorated. Her BNP level increased to 325.8 pg/mL. Therefore, we attempted aggressive fluid removal by hemodialysis for approximately 20 days. This reduced her weight by 10 kg, and her urine output gradually increased to 700–1,000 mL/day. Her serum Cr level improved to 1.9 mg/dL, and hemodialysis was discontinued on admission day 23. As diuresis was achieved, she had severe proteinuria, with massive protein secretion of 6–8 g/day. Her kidney biopsy revealed slight mesangial proliferation and absence of severe histological changes, such as adhesion or crescentic lesions, which are observed in progressive IgA nephropathy with severe proteinuria or AKI. She had very mild microscopic hematuria and mesangial deposits of IgA, which are occasionally observed in patients with minimal change disease (MCD). She had no history of macroscopic hematuria, which is often associated with reversible AKI in patients with IgA nephropathy. Clinical and pathological findings led to a diagnosis of AKI from MCD with mesangial IgA deposition. On admission day 25, intravenous methylprednisolone pulses (500 mg) were started, followed by 30 mg of oral prednisolone. At the beginning of steroid administration, her serum Cr and urine protein levels were 1.54 mg/dL and 6.4 g/day, respectively. One week thereafter, her urinary protein had decreased to <0.1 g/day, and the generalized edema had completely resolved. Her prednisolone dosage was tapered gradually over several months, and she has remained in complete remission without relapse (Fig. 2). Her serum Cr level improved to 0.9 mg/dL without a re-exacerbation of AKI.

Discussion

In the present case, aggressive fluid removal by hemodialysis was effective in achieving full recovery from AKI caused by MCNS despite the nephrotic state. Kidney biopsy was essential for making a precise diagnosis of the cause of AKI and determining the most appropriate treatment modality.

Patients with idiopathic NS sometimes have oliguric AKI as a complication [1]. Acute tubular necrosis, allergic interstitial nephritis, tubular obstruction by casts [6], and preexistence of arteriosclerosis [7] have also been reported as other pathological findings in AKI.

Hypovolemia has been widely accepted as the mechanism of AKI in MCD [6]. However, Lowenstein et al. [5] proposed an alternative hypothesis of hemodynamic disarrangement, namely the nephrosarca hypothesis. According to the nephrosarca hypothesis, interstitial edema results in increased hydrostatic pressure in the proximal renal tubules and Bowman's space, and this is responsible for the decreased glomerular filtration. Pathological changes have been suggested by kidney biopsy in some [5] but not all cases [7].

The treatment targets for NS with AKI are roughly divided into edema and proteinuria. In many patients, these targets can be achieved simultaneously, which is why it can be difficult to distinguish the main pathophysiological mechanism of AKI in NS [8]. In our case, AKI improved after volume reduction with dialysis, before NS treatment. Thus, the temporal clinical course of the present case supports the nephrosarca hypothesis.

Since hypovolemia is thought to be the most frequent cause of AKI, fluid administration is often initiated to improve renal perfusion (the so-called water challenge). However, it has recently become clear that hydration strategies, such as albumin administration and the water challenge, can cause kidney edema, leading to a worse prognosis [9]. Renal congestion is now believed to be the main mechanism of cardiorenal syndrome [10], i.e., renal venous and/or intra-abdominal hypertension induces interstitial edema, which attenuates the transglomerular pressure gradient and reduces renal perfusion. Volume overload caused by oliguric AKI possibly provokes renal congestion in the same manner as in cardiorenal syndrome. Interstitial edema due to NS is enhanced and exacerbated by renal congestion, which leads to more deleterious effects on renal perfusion. In the present case, it appears that aggressive volume withdrawal by hemodialysis helped to break this vicious cycle, leading to improvement of the severe oliguric AKI. In elderly patients, overhydration is especially important because they often have cardiac dysfunction. On the other hand, they are also susceptible to volume depletion due to pre-existing arteriosclerosis and nephron loss; thus, overzealous volume withdrawal using diuretics or by ultrafiltration must be avoided. Considering these factors, assessment of volume status is important for achieving prompt therapy, especially in elderly patients with NS complicated by oliguric AKI. Although change in body weight can be a convenient parameter for assessing volume status, it is often difficult to obtain the true "dry weight" and adequate hydration status. Onuigbo et al. [11] reported a case series of cardiorenal syndrome wherein renal function improved concomitantly with weight loss following intravenous diuretic administration. The authors speculated that an accelerated rise in pro-BNP level may predict a good outcome in aggressive decongestive therapy. In the present case, an increase in BNP level over a short period was observed, suggesting that this may be a useful parameter for the assessment of fluid status and efficacy of aggressive volume withdrawal.

Kidney biopsy is a useful means of determining the cause of AKI and identifying the most appropriate treatment for MCNS. Most patients with acute onset of NS and AKI may be pathologically diagnosed with MCD, and they tend to be empirically treated with corticosteroids. Many such patients entirely or partially recover from NS and AKI, with good outcomes. However, some patients, especially those with oliguria and advanced AKI (like the patient in the present case) have been reported to present with glomerular changes, steroid resistance, and lethal infections such as pneumonia and cellulitis, and may have a worse prognosis. Edematous tissue or organs may be susceptible to serious infection, and the harmful effects of corticosteroids may thus be intensified [6].

In addition to angiotensin-receptor blocker exposure and diarrhea, we suspect that the underlying severe arteriosclerotic lesion, which may have blunted the effect of the corticosteroid treatment, contributed to the further aggravation of kidney injury in the present case. Therefore, to investigate the etiology of AKI and NS, we performed a renal biopsy before administering corticosteroid therapy, after some fluid had been removed via hemodialysis to improve the patient's general condition.

Haas et al. [12] reported that one-third of patients older than 60 years who underwent kidney biopsy because of AKI were diagnosed with a condition that differed from the prebiopsy diagnosis. Moreover, diagnoses that might alter the therapeutic choice were more frequently made in patients with AKI and NS than in other patients [13]. Compared with membranous nephropathy and diabetic nephropathy, MCNS tends to be a less common cause of NS in elderly patients [14], but glucocorticoid treatment leads to complete remission at the same high frequency as that in younger patients [15]. However, inappropriate immunosuppression with steroids should be avoided because it can increase patients' susceptibility to infections. Taken together, these findings suggest that kidney biopsies are indispensable for an accurate diagnosis of the etiology of AKI and NS, particularly in elderly patients.

In conclusion, volume withdrawal by hemodialysis was effective in the present case of AKI caused by MCNS, and this supports the nephrosarca hypothesis. Appropriate fluid management is necessary, but injudicious administration of fluid, including albumin, must be avoided, especially in elderly patients who are at risk of overhydration. Kidney biopsies are useful in providing an accurate diagnosis, especially in elderly patients with AKI caused by MCNS.

Acknowledgments

The authors are grateful to N. Sakamoto, S. Tsuchida, M. Yoshinuma, and M. Igashima (Department of Pathology, Shinrakuen Hospital) for their technical assistance.

Statement of Ethics

Informed written consent for publication was obtained from the patient. The study was approved by the Ethics Committee of Koseiren Sanjo General Hospital (approval number: 12) and conducted in accordance with the World Medical Association Declaration of Helsinki.

Disclosure Statement

The authors have no conflict of interest to declare.

Funding Sources

None.

Author Contributions

Y. Oyama designed and wrote the manuscript. Y. Iwafuchi contributed to the concept and helped write the manuscript. T. Morioka performed the histological kidney examination. I. Narita supervised as a mentor.

References

1 Cameron JS. The nephrotic syndrome and its complications. Am J Kidney Dis. 1987 Sep;10(3):157–71.
2 Perico N, Remuzzi G. Edema of the nephrotic syndrome: the role of the atrial peptide system. Am J Kidney Dis. 1993 Sep;22(3):355–66.
3 Smith JD, Hayslett JP. Reversible renal failure in the nephrotic syndrome. Am J Kidney Dis. 1992 Mar;19(3):201–13.
4 Dorhout Mees EJ, Geers AB, Koomans HA. Blood volume and sodium retention in the nephrotic syndrome: a controversial pathophysiological concept. Nephron. 1984;36(4):201–11.
5 Lowenstein J, Schacht RG, Baldwin DS. Renal failure in minimal change nephrotic syndrome. Am J Med. 1981 Feb;70(2):227–33.
6 Chamberlain MJ, Pringle A, Wrong OM. Oliguric renal failure in the nephrotic syndrome. Q J Med. 1966 Apr;35(138):215–35.
7 Jennette JC, Falk RJ. Adult minimal change glomerulopathy with acute renal failure. Am J Kidney Dis. 1990 Nov;16(5):432–7.
8 Koomans HA. Pathophysiology of acute renal failure in idiopathic nephrotic syndrome. Nephrol Dial Transplant. 2001 Feb;16(2):221–4.
9 Perner A, Prowle J, Joannidis M, Young P, Hjortrup PB, Pettilä V. Fluid management in acute kidney injury. Intensive Care Med. 2017 Jun;43(6):807–15.
10 Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. J Card Fail. 2012 Dec;18(12):930–8.
11 Onuigbo MA, Agbasi N, Sengodan M, Rosario KF. Acute kidney injury in heart failure revisited – the ameliorating impact of "decongestive diuresis" on renal dysfunction in type 1 acute cardiorenal syndrome: accelerated rising Pro B natriuretic peptide is a predictor of good renal prognosis. J Clin Med. 2017 Aug;6(9):E82.
12 Haas M, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. Am J Kidney Dis. 2000 Mar;35(3):433–47.
13 Moutzouris DA, Herlitz L, Appel GB, Markowitz GS, Freudenthal B, Radhakrishnan J, et al. Renal biopsy in the very elderly. Clin J Am Soc Nephrol. 2009 Jun;4(6):1073–82.
14 Yokoyama H, Sugiyama H, Sato H, Taguchi T, Nagata M, Matsuo S, et al.; Committee for the Standardization of Renal Pathological Diagnosis and for Renal Biopsy and Disease Registry of the Japanese Society of Nephrology, and the Progressive Renal Disease Research of the Ministry of Health, Labour and Welfare of Japan. Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). Clin Exp Nephrol. 2012 Dec;16(6):903–20.
15 Donadio JV Jr. Treatment of glomerulonephritis in the elderly. Am J Kidney Dis. 1990 Oct;16(4):307–11.

Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2020;10:42–50

DOI: 10.1159/000507426

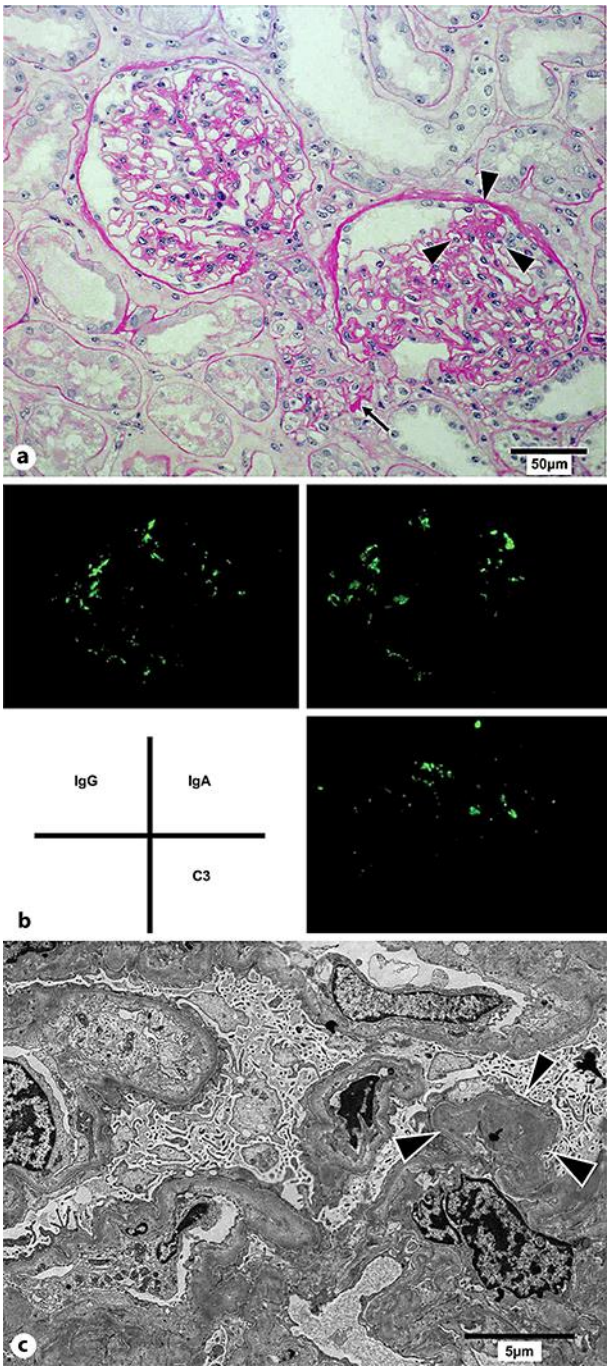

Fig. 1. **a** Light microscopy showing minor glomerular abnormalities and very mild segmental mesangial proliferation (arrowheads). Moderate hyalinosis of the artery is also seen (arrow). Periodic acid Schiff staining with original magnification ×400. **b** Faint and segmental positive immunostaining of IgA, IgG, and C3 in the mesangial area. **c** Electron microscopic examination revealing diffuse effacement of podocyte foot processes. Electron-dense deposits are seen in the paramesangial areas (arrowheads). Electron microscopy, original magnification ×2,500.

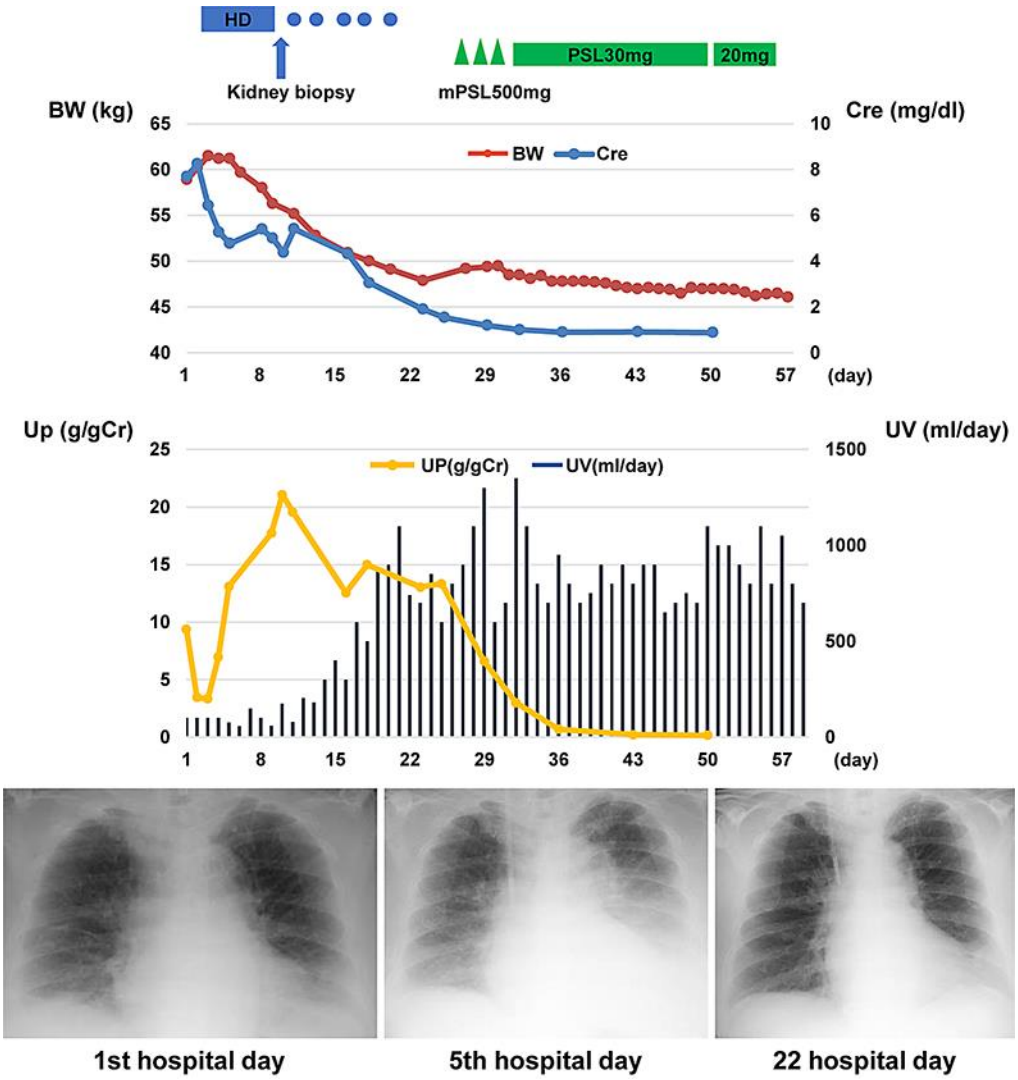

Fig. 2. Anasarca and cardiomegaly were aggravated for several days. Aggressive fluid removal by hemodialysis was effective for improving renal function. After the discontinuation of hemodialysis, prednisolone treatment was started, and complete remission of NS was achieved. BW, body weight; Cr, creatinine; HD, hemodialysis; mPSL, methylprednisolone; PSL, prednisolone; Up, urinary protein; UV, urinary volume.

Table 1. Laboratory data on admission

Complete blood count			Na	120	mEq/L	C3	151 (80–140)	mg/dL	**Urinalysis**		
WBC	15,700	/μL	K	6.7	mEq/L	C4	69.1 (11–34)	mg/dL	Specific gravity	1.030	
Neutro	96.1	%	Cl	89	mEq/L	CH50	62.0 (30–45)	IU/L	pH	5.5	
Lym	2.1	%	Ca	7.3	mg/dL	TSH	2.64	μIU/mL	Protein	(4+)	
Mono	1.7	%	IP	16.8	mg/dL	fT3	1.34	pg/mL	TP	9.38	g/gCr
Eosino	0.0	%	TP	5.7	g/dL	fT4	0.83	ng/dL	Glucose	(–)	
Baso	0.1	%	Alb	2.4	g/dL	MPO-ANCA	(–)		Occult blood	(±)	
Platelets	35.0×10^4	/μL	TC	351	mg/dL	PR3-ANCA	(–)		RBC	5–9	/HPF
RBC	455×10^4	/μL	TG	279	mg/dL	Anti-GBM Ab	(–)		WBC	5–9	/HPF
Hb	14.3	g/dL	LDL-C	130	mg/dL	ANA	(–)		Granular cast	1–4	/WF
Biochemistry			BS	116	mg/dL	HBV-Ag	(–)		Hyaline cast	1–4	/WF
AST	39	IU/L	HbA1c	5.7	%	HCV-Ab	(–)		NAG	171.5	U/l
ALT	42	IU/L	CRP	1.25	mg/dL	**Blood gas analysis**			β_2MG	65.2	μg/L
ALP	184	IU/L	IgG	994 (870–1,700)	mg/dL	pH	7.184		FENa	0.62	%
LDH	467	IU/L	IgA	473 (110–410)	mg/dL	HCO_3	7.7	mmol/L	Culture	*E. coli*	
γ-GTP	14	IU/L	IgM	67 (34–220)	mg/dL	BE	–19.4	mmol/L		*K. pneumoniae*	
CK	572	IU/L	IgE	2,589 (3.4–304)	IU/mL						
BUN	182.0	mg/dL	BNP	88.5	pg/mL						
Cr	7.70	mg/dL									

WBC, white blood cells; Neutro, neutrophils; Lym, lymphocytes; Mono, monocytes; Eosino, eosinophils; Baso, basophils; RBC, red blood cells; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; γ-GTP, gamma-guanosine triphosphate; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; IP, inorganic phosphate; TP, total protein; Alb, albumin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; BS, blood sugar; HbA1c, glycated hemoglobin; CRP, C-reactive protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; IgE, immunoglobulin E; BNP, brain natriuretic peptide; CH50, total complement; TSH, thyroid-stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibodies; PR3, proteinase 3; GBM Ab, glomerular basement membrane antibody; ANA, antinuclear antibody; HBV-Ag, hepatitis B virus antigen; HCV-Ab, hepatitis C virus antibody; HCO_3, bicarbonate; BE, base excess; NAG, N-acetyl glucosaminidase; β_2MG, β_2 microglobulin; FENa, fractional excretion of sodium.