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CASE REPORT

A case of secondary focal segmental glomerulosclerosis associated with malignant hypertension

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Abstract Focal segmental glomerulosclerosis (FSGS) is associated with various clinicopathological conditions, including hypertension. We report here a case of secondary FSGS associated with malignant hypertension. A 33-year-old man with a 1-month history of visual impairment and headache visited the Department of Ophthalmology at our hospital and was found to have hypertensive retinopathy and severe hypertension (230/160 mmHg). He was referred to our department based on suspected renal dysfunction. His blood pressure on admission was 250/130 mmHg. Physical examination and laboratory tests revealed hypertensive cardiac dysfunction, focal brain edema, renal dysfunction (serum creatinine, Cr 7.07 mg/dl, blood urea nitrogen, BUN 49.9 mg/dl), massive proteinuria (10.7 g/day), and thrombotic microangiopathy. Funduscopy showed exudate, hemorrhage, and papilledema. The cause of secondary hypertension could not be identified. He was treated for primary malignant hypertension, but required hemodialysis 3 days after admission due to anuria. Treatment with antihypertensive agents resulted in the gradual recovery of renal function, although heavy proteinuria continued with nephrotic syndrome. Renal biopsy performed 1 month after admission showed features of malignant nephrosclerosis with secondary FSGS. Hemodialysis was discontinued following further improvement in renal function and the most recent laboratory tests showed proteinuria 1.8 g/day and persistent renal dysfunction (BUN 36.5 mg/dl, Cr 3.14 mg/dl). Malignant hypertension may cause various injuries, including glomerular endothelial and epithelial cell injuries in glomerular hypertension and hyperfiltration, increase of the renin–angiotensin–aldosterone system, and endothelial–epithelial interaction, resulting in the development of secondary FSGS and heavy proteinuria.

Keywords Focal segmental glomerulosclerosis · Malignant hypertension · Malignant nephrosclerosis · Hypertensive emergency · Nephrotic syndrome · Thrombotic microangiopathy

Introduction

Hypertensive emergency is a condition in which elevated blood pressure results in the injury of various organs, such as the cardiovascular system, central nervous system, and renal system [1–3]. Malignant hypertension with severe papilledema requires immediate management [3]. Malignant hypertension may be diagnosed incidentally without any history of hypertension, or may be preceded by a period of essential hypertension [3–5]. Significant proteinuria is an uncommon finding in patients with benign nephrosclerosis associated with essential hypertension. In contrast, malignant hypertension often causes proteinuria, which can sometimes reach the levels seen in nephrotic syndrome [4, 5]. Hypertension is one of the etiological factors of secondary focal segmental glomerulosclerosis

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(FSGS), which is mediated by adaptive structural–functional changes and associated initially with normal renal mass [4–7]. However, the pathology of the kidney in patients with hypertension and heavy proteinuria is still uncertain.

Here, we report a case of secondary FSGS associated with malignant hypertension in a patient with malignant hypertension, retinopathy, hemolytic anemia, and renal dysfunction with nephrotic syndrome.

Case report

A 32-year-old Japanese man presented with a 1-month history of visual disturbance, headache, and loss of appetite. He had been diagnosed with essential hypertension 10 years earlier, but did not take any medications. He had a history of moderate intake of alcohol (drinking alcohol on weekends) and no history of smoking or drug abuse. The family history included a hypertensive father who died of cerebral hemorrhage at 46 years of age. The patient visited an ophthalmologist at our hospital for persistent visual disturbance and headache. He was found to have severe hypertension (230/160 mmHg) and hypertensive retinopathy, and was referred to our department for further management.

The patient was alert on admission. His height was 172 cm and body weight was 65 kg. His blood pressure was 250/130 mmHg, pulse rate 125 beats/min, and body temperature 37.3 °C. Physical examination showed systolic heart murmur (LEVINE II/VI), and pretibial edema. Visual activity showed numerous digitorum (counting finger), and funduscopy revealed stage IV on the Keith–Wagener classification, including findings of exudates, blot hemorrhages, and papilledema. Chest X-ray showed cardiomegaly (cardiothoracic ratio = 52.2 %), and echocardiography indicated systolic cardiac dysfunction (ejection fraction = 56 %, ventricular asynergy in inferior left ventricular wall, and small pericardial effusion). The plasma level of brain natriuretic peptide was elevated (3989.5 pg/ml). These findings indicated hypertensive cardiac dysfunction. Neurological examination showed no focal signs, but head computed tomography (CT) and magnetic resonance imaging (MRI) revealed focal edema in the pons and white matter of the frontal and occipital lobes.

Serum levels of creatinine (Cr 7.07 mg/dl), blood urea nitrogen (BUN 49.9 mg/dl), and uric acid (8.4 mg/dl) were elevated. Urinalysis showed 4+ proteinuria (10.7 g/day), 3+ hematuria (50–99 erythrocytes/high-power field), no sugar, various sediments, and urinary oval fat bodies (10–19/whole field). Urinary β2-microglobulin concentration was 2291 μg/ml. Serum levels of total protein (6.2 g/dl) and serum albumin (3.1 g/dl) were slightly decreased, and total cholesterol (263 mg/dl) and LDL cholesterol (160 mg/dl) were slightly elevated. These findings indicated renal dysfunction with nephrotic syndrome-like status. Blood analysis also showed hemolytic anemia with thrombocytopenia (erythrocyte count 362 $\times$ 10^4/μl, hemoglobin 11.9 mg/dl, hematocrit 33.5 %, platelet count 11.6 $\times$ 10^4/μl, and haptoglobin 3.0 mg/dl), but ADAMTS13 activity (98 %) was within the normal range. Serological survey showed normal levels of immunoglobulins, complement, antinuclear antibody, and antineutrophil cytoplasmic antibody. Table 1 summarizes the laboratory data on admission.

Based on these findings, he was diagnosed as malignant hypertension with multiple organ damage, including the cardiovascular system, central nervous system, and renal system. The patient was treated with intravenous nicardipine, a calcium channel blocker (Fig. 1). However, he developed anuria on day 2 after admission with elevation of serum Cr level to 9.4 mg/dl, requiring hemodialysis from days 3 to 39. From day 4, his urine volume started to recover gradually.

The cause of malignant hypertension was investigated. Plasma renin and aldosterone were high (renin activity >20 ng/ml/h, active form renin 363.8 pg/ml, aldosterone 302.9 pg/ml). Hormonal assays showed slightly elevated dopamine (54 pg/ml) and noradrenaline (625 pg/ml), but normal adrenaline (47 pg/ml). The urinary catecholamine level was within the normal range. Abdominal CT and MRI showed no atrophic changes in both kidneys. Magnetic resonance angiography showed apparently normal left and right renal arteries. Thus, blood and urinary laboratory tests and the imaging studies failed to detect any cause of hypertension. Therefore, the diagnosis was considered to be primary (essential) malignant hypertension. The laboratory data related to malignant hypertension are summarized in Table 2.

Since the first day of admission, the patient was placed on antihypertensive medications, including calcium channel blocker (nifedipine 20–60 mg) and angiotensin II receptor blocker (ARB, olmesartan 10–20 mg) (Fig. 1). The blood pressure fell to 150/94 mmHg, but proteinuria remained within the nephrotic range (3.2 g/day), and serum albumin level gradually decreased to 2.1 g/dl, with an increase in the total cholesterol (263 mg/dl), indicating the development of nephrotic syndrome.

During hemodialysis under a stable blood pressure level, renal biopsy was performed 29 days after admission in order to determine the renal prognosis and the pathological changes associated with the nephrotic syndrome. Examination of the renal biopsy sample showed prominent changes in the renal arteries (Fig. 2). Marked intimal fibrosis with onion-skin lesions were noted in numerous arterioles, consistent with malignant hypertension. The biopsy material contained 19 glomeruli; 1 was obsolete and

Table 1 Laboratory findings on admission

Blood cell counts		ANA (times)	<40
RBC ($\times 10^4$/μl)	362	MPO-ANCA (EU)	<10
Hb (g/dl)	11.9	PR3-ANCA (EU)	<10
Ht (%)	33.5	Anti-Scl70 Ab (U/ml)	<7.0
WBC (μl)	8900	ACA (index)	<5.0
PLTs ($\times 10^4$/μl)	11.6	Anti-GBM ab (EU)	<10
Biochemistry		ASK (μg/ml)	9.1
CRP (mg/dl)	1.28	ASO (IU/ml)	105
BUN (mg/dl)	49.9	Coagulation system	
Cre (mg/dl)	7.07	PT (s)	13.1
UA (mg/dl)	8.4	APTT (s)	30.4
T-Prot (g/dl)	6.2	Fibrinogen (mg/dl)	580
Alb (g/dl)	3.1	FDP (μg/dl)	9.1
T-Cho (mg/dl)	263	D-dimer (μg/dl)	2.8
TG (mg/dl)	167	Haptoglobin (mg/dl)	3.0
LDL (mg/dl)	160	Indirect antiglobulin test	(–)
AST (IU/L)	29	Direct antiglobulin test	(–)
ALT (IU/L)	12	ADAMTS13 activity (%)	98
LDH (IU/L)	948	Urinalysis	
T-Bil (mg/dl)	1.1	Proteinuria	4+
Na (mEq/L)	138	Protein (g/day)	10.7
K (mEq/L)	3.0	Occult blood	3+
Cl (mEq/L)	98	Urine glucose	(–)
Ca (mg/dl)	8.5	RBC (cells/HPF)	50–99
P (mg/dl)	6.2	Hyaline casts (cast/WF)	10–19
Glucose (mg/dl)	87	Granular cast (cast/WF)	30–49
HbA1c (%)	4.1	Waxy cast (cast/WF)	30–49
Ferritin (ng/dl)	899.4	Epithelial casts (cast/WF)	10–19
C3 (mg/dl)	134	Fatty cast (cast/WF)	10–19
C4 (mg/dl)	43	Oval fat body (cast/WF)	10–19
CH50 (U/ml)	59.7	Urine β2MG (μg/dl)	2291

RBC red blood cells, *Hb* hemoglobin, *Ht* hematocrit, *WBC* white blood cells, *PLTs* platelets, *CRP* C-reactive protein (<0.3 mg/dl), *UA* uric acid, C3 (80–150 mg/dl), C4 (15–40 mg/dl), CH50 (32–44 U/ml), *ANA* antinuclear antigen (<40×), *MPO-ANCA* myeloperoxidase antineutrophil cytoplasmic antibody, *PR3-ANCA* proteinase 3-ANCA, *Anti-Scl70 Ab* antiscleroderma antibody (<10.0 U/ml), *ACA* anticentromere antibody (index <16.0), *anti-GBM Ab* antiglomerular basement membrane antibody, *ASK* antistreptokinase, *ASO* antistreptolysin O, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *FDP* fibrin degradation products, *ADAMS13* a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13 (40–150 %), *HPF* high-power field, *WF* whole field, *β2MG* β2-microglobulin

5 tended to show glomerular collapse with wrinkled glomerular basement membrane. In addition, 3 glomeruli showed segmental glomerular hypercellularity with foam cell infiltration and hyperplasia of epithelial cells in Bowman's space, resembling the features of FSGS, the cellular variant in the Columbia classification. The remaining glomeruli showed minor glomerular abnormalities. Tubular atrophy and interstitial fibrosis were also noted. Immunostaining for CD34, CD68, and α-smooth muscle actin (α-SMA) showed that segmental glomerular sclerotic lesions were characterized by the loss of $CD34^+$ glomerular capillaries with $CD68^+$ infiltrating macrophages and α-SMA^+ activated mesangial cells (Fig. 3). Hyperplastic epithelial cells in Bowman's capsule showed loss of podocyte marker (CD10) and the expression of parietal epithelial cell marker (AE1/AE3). Immunofluorescence examination showed focal segmental deposition of IgM, C3, and C1q in segmental sclerotic lesions, although no deposition of IgG, IgA, C3, or C4 was noted in glomeruli. Electron microscopic examination showed diffuse injury of glomerular capillary endothelial cells, focal effacement of podocyte foot processes, and focal detachment of podocytes from the glomerular basement membrane (Fig. 4). The final diagnosis was malignant nephrosclerosis and secondary FSGS.

Treatment with a calcium channel blocker (nifedipine 60 mg), ARB (olmesartan 40 mg), β-blocker (atenolol 50 mg), and renin inhibitor (aliskiren 150 mg) continued, and the patient's renal function showed gradual recovery, allowing the discontinuation of hemodialysis (Fig. 1). The most recent measures of renal function were BUN of 36.5 mg/dl, Cr 3.14 mg/dl, and proteinuria 1.8 g/day, without hemodialysis.

Discussion

We have reported a case of malignant hypertension with nephrotic syndrome and renal dysfunction. Renal biopsy showed FSGS lesions and endothelial cell injury in addition to typical features of malignant nephrosclerosis. We consider that the nephrotic syndrome in this patient was associated with the development of secondary FSGS in malignant hypertension. Antihypertensive therapy, including ARB, rescued renal dysfunction and nephrotic syndrome. Although the characteristic pathology of hypertensive nephropathy with nephrotic-range proteinuria remains uncertain, secondary FSGS should be considered in patients with malignant hypertension and nephrotic-range proteinuria.

In malignant hypertension, many patients present with hematuria and proteinuria, and some patients show nephrotic-range heavy proteinuria [4, 5]. Since hypertension is considered to be an etiological factor of secondary FSGS [6, 7], it is conceivable that secondary FSGS develops in malignant hypertension with nephrotic syndrome. Although several experimental animal studies concerning malignant hypertension and the formation of FSGS lesions in the kidney have been reported [8–11], the clinical studies of the kidney histology in malignant hypertension have generally not emphasized the prominence of FSGS [4, 5]. Only a few clinical studies described

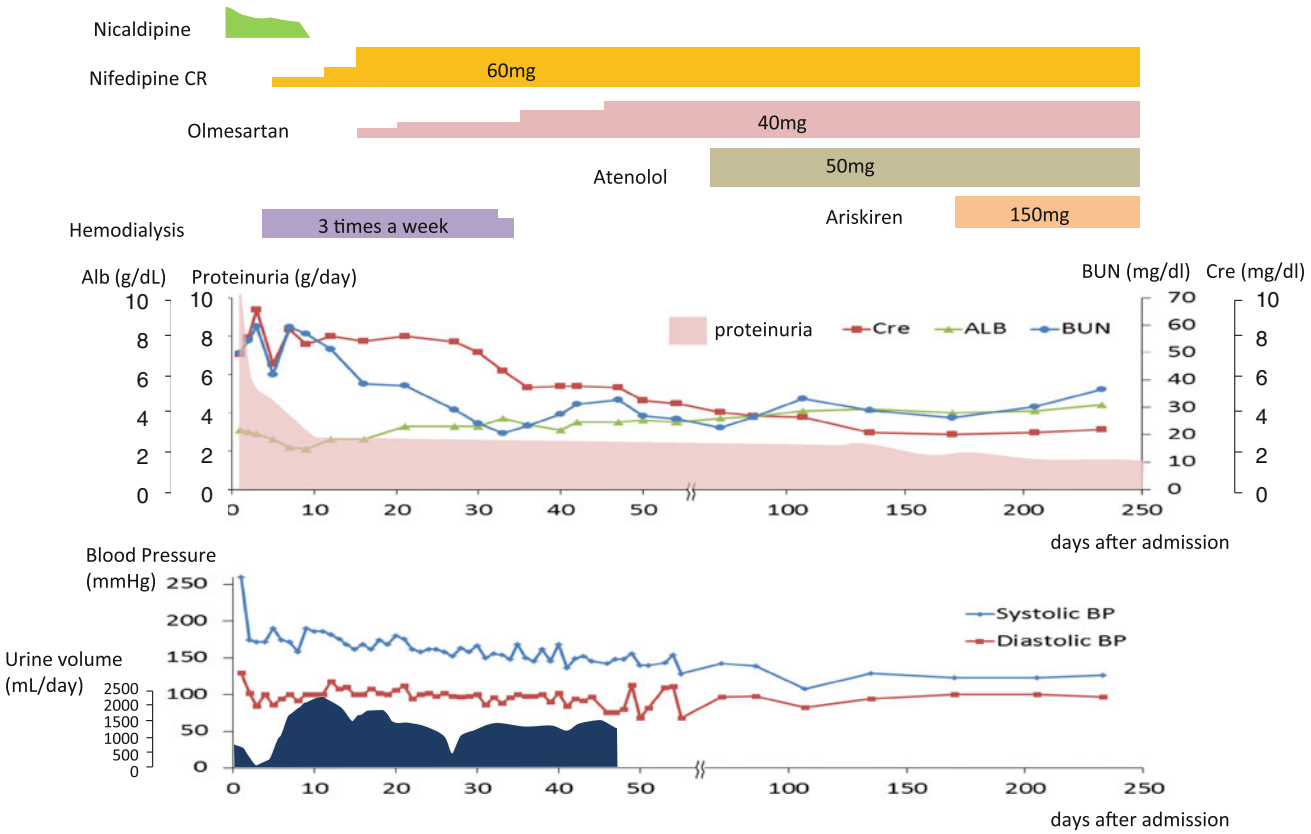

Fig. 1 Clinical course. Malignant hypertension, renal dysfunction, and nephrotic syndrome were present in the early period after admission. Hemodialysis was performed between days 3 and 39. Treatment of malignant hypertension resulted in a decrease in blood pressure and gradual recovery of renal function to mild-to-moderate renal dysfunction, allowing discontinuation of hemodialysis and resolution of the nephrotic syndrome to about 2.0 g/day of proteinuria

the development of FSGS in malignant hypertension [12–14], and these studies reported that FSGS may occur in primary malignant hypertension with nephrotic-range proteinuria, and may contribute to renal dysfunction. In addition, a few cases of renal artery stenosis with malignant hypertension and nephrotic syndrome have been reported [15–20]. In such cases, histopathological examination of the contralateral kidney often shows lesions of FSGS with benign or malignant nephrosclerosis. In the present case, we did not detect conditions that could cause secondary hypertension, such as renovascular stenosis. The diagnosis of renal biopsy was, therefore, essential (primary) malignant nephrosclerosis with secondary FSGS.

Three mechanisms can be involved in the development of secondary FSGS in patients with malignant hypertension: glomerular hypertension and hyperfiltration, activation of the renin–angiotensin II–aldosterone system, and glomerular endothelial cell injury.

Hemodynamic factors are generally believed to play an important role in the development of secondary FSGS [6, 7, 21–24]. The most important causes of secondary FSGS are conditions associated with high intraglomerular filtration pressure, including uncontrolled severe hypertension. In addition, loss of functioning nephrons may contribute to the augmentation of glomerular hypertension and hyperfiltration [6, 7, 24]. Since 6 out of 19 glomeruli showed global sclerosis or glomerular collapse with glomerular ischemia in the renal biopsy samples, glomerular hyperfiltration after loss of functioning nephrons also developed in the present case. Glomerular ischemia and collapse is also known as one of the etiologies of secondary FSGS, such as arteriosclerosis and cholesterol embolism [6, 7, 25]. In our case, however, FSGS lesions developed mainly in non-collapse glomeruli. We, therefore, considered that the glomerular hypertension and hyperfiltration in malignant hypertension and secondary to nephron loss might contribute to the podocyte injury, as well as the development of secondary FSGS lesions.

Molecular pathogenesis, i.e., activation of the renin–angiotensin–aldosterone system, may play a role in the damage associated with hyperfiltration injury [26–28]. Malignant hypertension is usually accompanied by a high secretion of renin by the kidney, which is not downregulated by the rise in blood pressure. In addition, local tissue

Table 2 Laboratory data concerning malignant hypertension

Plasma	
Cortisol (4.0–18.3 μg/dl)	12.0
ACTH (7.2–63.3 pg/ml)	13.3
TSH (μIU/ml)	3.560
FT3 (pg/ml)	2.84
FT4 (ng/dl)	1.07
Plasma renin activity (0.3–2.9 ng/ml/h)	>20
Active renin (2.5–21 pg/ml)	363.8
Aldosterone (29.9–159 pg/ml)	302.9
Adrenaline (<100 pg/ml)	47
Noradrenaline (100–450 pg/ml)	625
Dopamine (<20 pg/ml)	54
Urine	
Urine adrenaline (3.4–26.9 μg/day)	8.2
Urine noradrenaline (48.6–168.4 μg/day)	102.5
Urine dopamine (365.0–961.5 μg/day)	197.0
Urine HVA (2.1–6.3 mg/day)	0.57
Urine VMA (1.5–4.3 mg/day)	4.04

ACTH adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone, *FT3* free triiodothyronine, *FT4* free thyroxine, *Urine HVA* urine homovanillic acid, *Urine VMA* urine vanillylmandelic acid

angiotensin II is also activated in renal angiotensin-converting enzyme [29]. Angiotensin II contributes to systemic hypertension by constricting the efferent arterioles, causing an increase in intraglomerular pressure and filtration fraction. In addition, angiotensin II also acts directly on the endothelial cells as well as podocyte injury to result in the development of glomerular disease [26–28]. Indeed, in a rat model, angiotensin II-dependent hypertension exhibits endothelial cells and podocyte injury as well as secondary FSGS [11]. The present case indicates that glomerular hypertension and hyperfiltration as well as activation of the renin–angiotensin system may be mediated by secondary FSGS, because the present case of malignant hypertension with nephrotic syndrome was treated successfully with antihypertensive agents, including ARB.

Glomerular endothelial cell injury could also have contributed to the secondary FSGS in the present case. Malignant nephrosclerosis is considered to be a form of thrombotic microangiopathy [4, 5]. The extremely high blood pressure in patients with malignant hypertension can cause direct injury of the endothelium, probably shear stress injury, with the activation of endothelial cells, in small arteries and glomeruli. In our case, hemolysis was

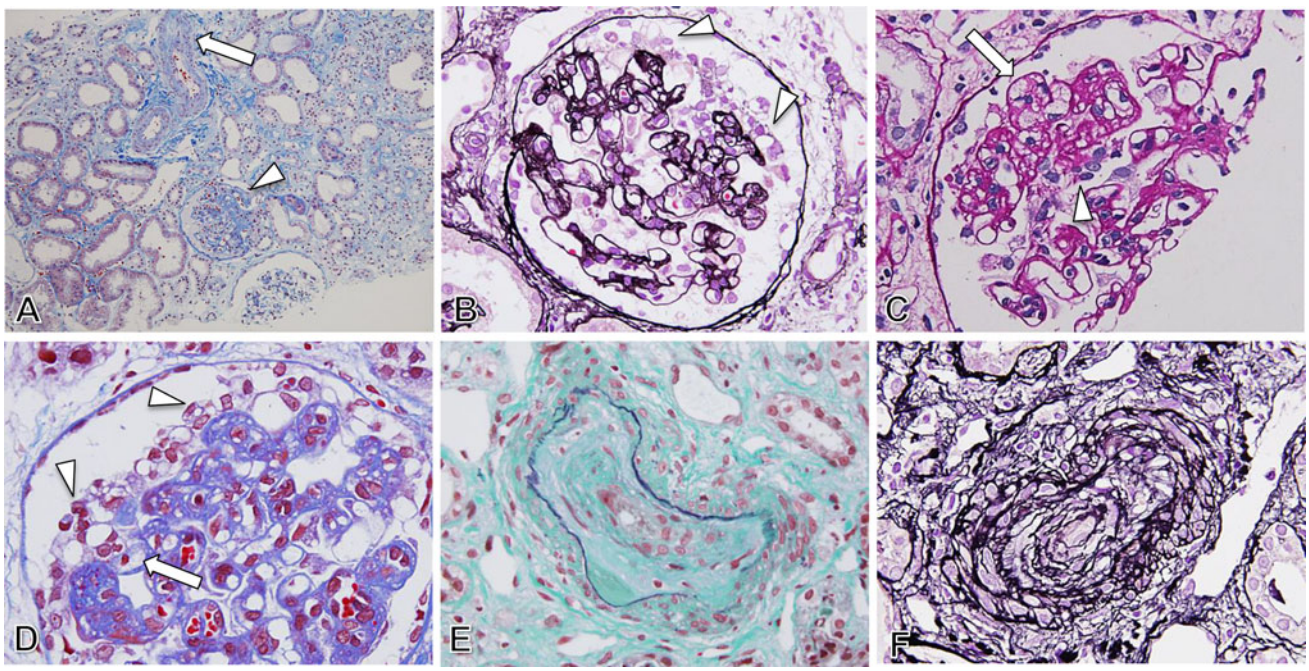

Fig. 2 Light microscopy (**a**, **d** Masson trichrome stain **b**, **f** periodic acid silver methenamine stain, **c** periodic acid-Schiff stain, **e** elastica Masson-Goldner stain; magnification: **a** ×200, **b** ×600, **c**–**f** ×800). Renal biopsy specimens showed marked thickening of the intima of the arterioles (*arrow* in **a**) and segmental sclerosis (*arrowhead* in **a**). About 60 % of the interstitium showed atrophy of the renal tubules with fibrosis. In one glomerulus, hyperplasia of epithelial cells was detected in Bowman's space (*arrowheads* in **b**). Two glomeruli showed segmental endocapillary hypercellularity with infiltration of foam cells (*arrows* in **c** and **d**) and hyperplasia of epithelial cells in Bowman's space (*arrowheads* in **c** and **d**). Arterioles showed marked intimal thickening without elastosis (**e**) but with intimal fibrosis (also known as onion-skin lesion) (**f**)

present from the admission. Although hemodialysis might influence the augmentation of glomerular endothelial cell injury in renal biopsy findings, we considered that the major mechanism of endothelial cell injury in our case was associated with malignant hypertension. Electron microscopy showed diffuse and global endothelial cell injury in glomeruli. Endothelial injury may result in switching from the endothelial anticoagulant phenotype to the procoagulant phenotype, which is characterized by decreased fibrinolytic activity, including the upregulation of plasminogen activator inhibitor-1, exposure of the thrombogenic subendothelial surface, platelet activation, and cellular activation

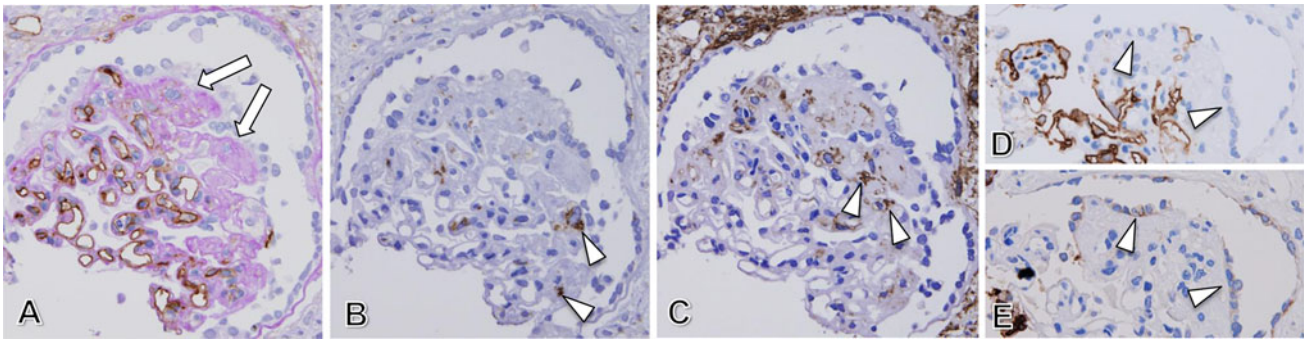

Fig. 3 Immunohistochemical examination of representative glomeruli with segmental sclerosis (**a** staining for CD34; **b** staining for CD68; **c** staining for α-smooth muscle actin, α-SMA; **d** staining for CD10; **e** staining for AE1/AE3; magnification: **a**–**e** ×800). The segmental sclerotic lesion was characterized by the loss of $CD34^+$ glomerular capillaries (*arrows* in **a**) with increased deposition of glomerular extracellular matrix and presence of $CD68^+$ macrophages (*arrowheads* in **b**) and α-SMA^+ activated mesangial cells (*arrowheads* in **c**). Hyperplastic epithelial cells on segmental sclerosis were characterized by the loss of normal podocyte marker CD10 and the expression of Bowman's epithelial cell marker cytokeratin (AE1/AE3)

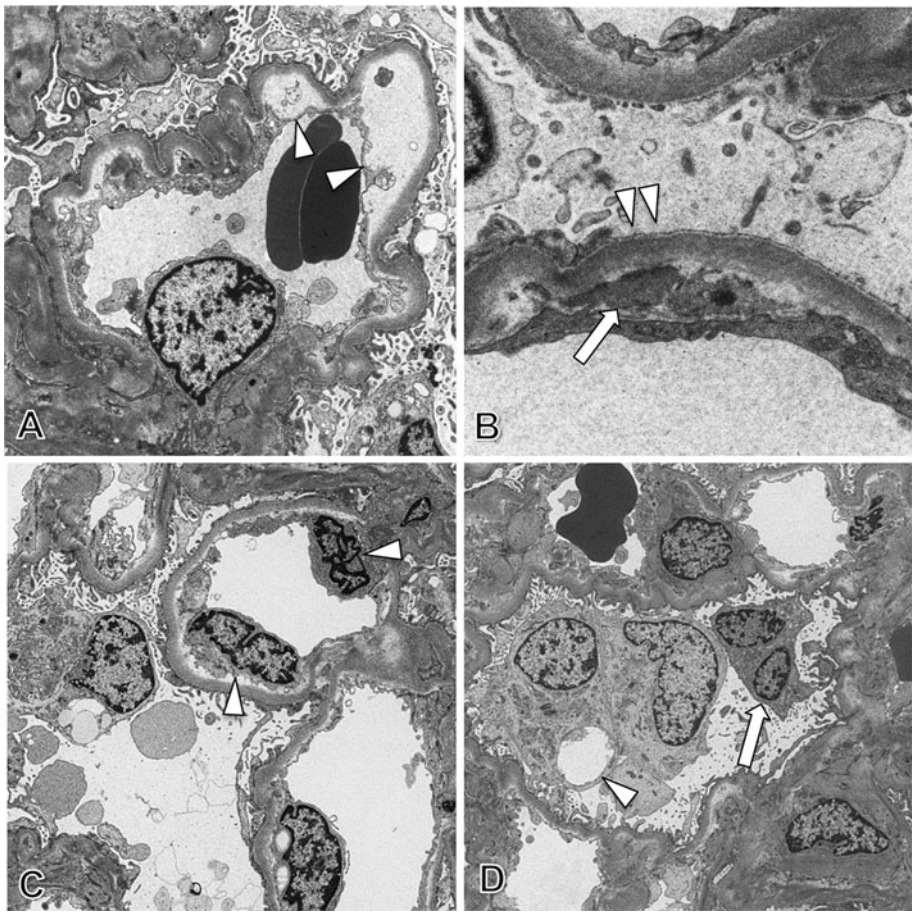

Fig. 4 Electron microscopy (magnification: **a** ×8,000, **b** ×20,000, **c**, **d** ×7,000). Diffuse glomerular endothelial cell injury was detected, which was characterized by diffuse widening of the subendothelial space (*arrowheads* in **a**) with mesangial interposition (*arrow* in **b**), increased number of endothelial cells with swelling of the cytoplasm (*arrowheads* in **c**), and loss of fenestrae in glomerular capillaries. Segmental injury of glomerular epithelial cells was also noted, which was characterized by focal detachment of podocytes from the glomerular basement membrane (*arrowheads* in **b**), focal effacement of the foot processes, villi formation, two nuclei per podocyte (*arrow* in **d**), and vacuolar formation in the podocyte cytoplasm (*arrowhead* in **d**)

with upregulation of adhesion molecules, chemokines, cytokines, and transcription factors [30–32]. Infiltration of macrophages and foam cell differentiation with the production of several cytokines also develops in the glomeruli after endothelial cells and podocyte injury [33–36]. Combined, all these factors may contribute to podocyte damage. The exact mechanisms of how endothelial injury contributes to FSGS are not fully understood, but it is assumed that endothelial cell injury probably leads to podocyte damage through endothelial–podocyte interaction [37, 38].

In summary, the present case serves as a reminder that the development of secondary FSGS in malignant nephrosclerosis should be considered in patients with severe hypertension and nephrotic-range proteinuria. It also illustrates the importance of hemodynamic factors, including glomerular hypertension and hyperfiltration, activation of the renin–angiotensin–aldosterone system, and glomerular endothelial cell injury, in glomerular injury and podocyte damage, leading to the development of secondary FSGS in malignant hypertension. The results also emphasize the importance of both the control of blood pressure and the inhibition of the renin–angiotensin–aldosterone system in the management of nephrotic syndrome with malignant hypertension.

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Conflict of interest All the authors have declared no competing interest.

References

1. Rosei EA, Salvetti M, Farsang C. Treatment of hypertensive urgencies and emergencies. Blood Press. 2006;15:255–6.
2. Marik PE, Rivera R. Hypertensive emergencies: an update. Curr Opin Crit Care. 2011;17:569–80.
3. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H; Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Hypertens Res. 2009;32:3–107.
4. Olson JL. Renal disease caused by hypertension. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, editors. Heptinstall's pathology of the kidney. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 937–90.
5. D'Agati VD, Jennette JC, Silva FG. Hypertensive nephrosclerosis, renal artery stenosis, and atheroembolization. In: D'Agati VD, Jennette JC, Silva FG, editors. Atlas of nontumor pathology: non-neoplastic kidney diseases. Washington, DC: American Registry of Pathology; 2005. p. 425–546.
6. Rennke HG, Klein PS. Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. Am J Kidney Dis. 1989;13:443–56.
7. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43:368–82.
8. Kuijpers MH, Gruys E. Spontaneous hypertension and hypertensive renal disease in the fawn-hooded rat. Br J Exp Pathol. 1984;65:181–90.
9. Saito T, Sato H, Obara K, Yamakage K, Abe K, Furuyama T, Yoshinaga K. Progression of experimental focal glomerulosclerosis in the spontaneously hypertensive rat. J Lab Clin Med. 1990;115:165–73.
10. Shimokama T, Haraoka S, Horiguchi H, Sugiyama F, Murakami K, Watanabe T. The Tsukuba hypertensive mouse (transgenic mouse carrying human genes for both renin and angiotensinogen) as a model of human malignant hypertension: development of lesions and morphometric analysis. Virchows Arch. 1998;432:169–75.
11. Vernerová Z, Kujal P, Kramer HJ, Bäcker A, Cervenka L, Vanecková I. End-organ damage in hypertensive transgenic Ren-2 rats: influence of early and late endothelin receptor blockade. Physiol Res. 2009;58(Suppl 2):S69–78.
12. Jones DB. Arterial and glomerular lesions associated with severe hypertension. Light and electron microscopic studies. Lab Invest. 1974;31:303–13.
13. Harvey JM, Howie AJ, Lee SJ, Newbold KM, Adu D, Michael J, Beevers DG. Renal biopsy findings in hypertensive patients with proteinuria. Lancet. 1992;340:1435–6.
14. Kadiri S, Thomas JO. Focal segmental glomerulosclerosis in malignant hypertension. S Afr Med J. 2002;92:303–5.
15. Fujii S, Kasahara H, Oguchi H. A case of renovascular hypertension with nephrotic syndrome, accompanied by focal segmental glomerulosclerosis-like lesion in the contralateral kidney. Nihon Jinzo Gakkai Shi. 1991;33:1017–24 (Japanese).
16. Ubara Y, Hara S, Katori H, Yamada A, Morii H. Renovascular hypertension may cause nephrotic range proteinuria and focal glomerulosclerosis in contralateral kidney. Clin Nephrol. 1997;48:220–3.
17. Alkhunaizi AM, Chapman A. Renal artery stenosis and unilateral focal and segmental glomerulosclerosis. Am J Kidney Dis. 1997;29:936–41.
18. Bhowmik D, Dash SC, Jain D, Agarwal SK, Tiwari SC, Dinda AK. Renal artery stenosis and focal segmental glomerulosclerosis in the contralateral kidney. Nephrol Dial Transplant. 1998;13:1562–4.
19. Alchi B, Shirasaki A, Narita I, Nishi S, Ueno M, Saeki T, Miyamura S, Gejyo F. Renovascular hypertension: a unique cause of unilateral focal segmental glomerulosclerosis. Hypertens Res. 2006;29:203–7.
20. Hijazi R, Chandar J, Nwobi O, Muneeruddin S, Zilleruelo G, Abitbol CL. Renal manifestations in toddlers with Takayasu's arteritis and malignant hypertension. Pediatr Nephrol. 2009;24:1227–30.
21. Nagata M, Kriz W. Glomerular damage after uninephrectomy in young rats. II. Mechanical stress on podocytes as a pathway to sclerosis. Kidney Int. 1992;42:148–60.
22. Rennke HG. How does glomerular epithelial cell injury contribute to progressive glomerular damage? Kidney Int Suppl. 1994;45:S58–63.
23. Kriz W, Kretzler M, Nagata M, Provoost AP, Shirato I, Uiker S, Sakai T, Lemley KV. A frequent pathway to glomerulosclerosis: deterioration of tuft architecture-podocyte damage-segmental sclerosis. Kidney Blood Press Res. 1996;19:245–53.
24. D'Agati VD. Podocyte injury in focal segmental glomerulosclerosis: lessons from animal models (a play in five acts). Kidney Int. 2008;73:399–406.

25. Thadhani R, Pascual M, Nickeleit V, Tolkoff-Rubin N, Colvin R. Preliminary description of focal segmental glomerulosclerosis in patients with renovascular disease. Lancet. 1996;347:231–3.
26. Durvasula RV, Shankland SJ. The renin–angiotensin system in glomerular podocytes: mediator of glomerulosclerosis and link to hypertensive nephropathy. Curr Hypertens Rep. 2006;8:132–8.
27. Suzuki K, Han GD, Miyauchi N, Hashimoto T, Nakatsue T, Fujioka Y, Koike H, Shimizu F, Kawachi H. Angiotensin II type 1 and type 2 receptors play opposite roles in regulating the barrier function of kidney glomerular capillary wall. Am J Pathol. 2007;170:1841–53.
28. Sofue T, Kiyomoto H, Kobori H, Urushihara M, Nishijima Y, Kaifu K, Hara T, Matsumoto S, Ichimura A, Ohsaki H, Hitomi H, Kawachi H, Hayden MR, Whaley-Connell A, Sowers JR, Ito S, Kohno M, Nishiyama A. Early treatment with olmesartan prevents juxtamedullary glomerular podocyte injury and the onset of microalbuminuria in type 2 diabetic rats. Am J Hypertens. 2012;25:604–11.
29. Ichihara A, Kobori H, Nishiyama A, Navar LG. Renal renin–angiotensin system. Contrib Nephrol. 2004;143:117–30.
30. Fogo AB. Mechanisms in nephrosclerosis and hypertension—beyond hemodynamics. J Nephrol. 2001;14(Suppl 4):S63–9.
31. Hertig A, Rondeau E. Role of the coagulation/fibrinolysis system in fibrin-associated glomerular injury. J Am Soc Nephrol. 2004; 15:844–53.
32. Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am Soc Nephrol. 2004;15:1983–92.
33. Imakiire T, Kikuchi Y, Yamada M, Kushiyama T, Higashi K, Hyodo N, Yamamoto K, Oda T, Suzuki S, Miura S. Effects of renin–angiotensin system blockade on macrophage infiltration in patients with hypertensive nephrosclerosis. Hypertens Res. 2007;30:635–42.
34. Ikezumi Y, Suzuki T, Karasawa T, Kawachi H, Nikolic-Paterson DJ, Uchiyama M. Activated macrophages down-regulate podocyte nephrin and podocin expression via stress-activated protein kinases. Biochem Biophys Res Commun. 2008;376:706–11.
35. Wang Y, Harris DC. Macrophages in renal disease. J Am Soc Nephrol. 2011;22:21–7.
36. Matsumoto K, Fukuda N, Abe M, Fujita T. Dendritic cells and macrophages in kidney disease. Clin Exp Nephrol. 2010;14:1–11.
37. Hauser PV, Collino F, Bussolati B, Camussi G. Nephrin and endothelial injury. Curr Opin Nephrol Hypertens. 2009;18:3–8.
38. Henao DE, Saleem MA, Cadavid AP. Glomerular disturbances in preeclampsia: disruption between glomerular endothelium and podocyte symbiosis. Hypertens Pregnancy. 2010;29:10–20.