【 CASE REPORT 】

Nephrotic Syndrome Associated with Buerger's Disease

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Abstract:
We herein report a 43-year-old woman with Buerger's disease who presented with nephrotic syndrome, renal dysfunction, and mild hypertension. A kidney biopsy revealed focal segmental glomerulosclerosis (FSGS), but there were no findings associated with frequent secondary FSGS or a history of long-term hypertension. A small focal renal infarction was seen on ^{99m}Tc-dimercaptosuccinic acid renal scintigraphy, suggesting that FSGS was due to renal microinfarction associated with Buerger's disease. After the commencement of angiotensin-converting enzyme inhibitor therapy, the hypertension immediately improved, along with significant attenuation of proteinuria. Renal ischemia by vasoconstriction of the glomerular efferent arterioles in association with Buerger's disease may result in glomerular hyperfiltration followed by FSGS.

Key words: Buerger's disease, nephrotic syndrome, focal segmental glomerulosclerosis, glomerular hyperfiltration, renal ischemia, renin-angiotensin system

Introduction

Buerger's disease is a nonatherosclerotic, segmental, inflammatory vasculitis strongly associated with smoking. Buerger's disease primarily affects the small and medium arteries of the upper and lower extremities. However, in rare cases, it can also affect visceral blood vessels, including the cerebral, coronary, renal, mesenteric, and internal thoracic arteries (1, 2). Other symptoms, including renal infarction and renal artery stenosis, have been observed via angiography, histopathology, and autopsies (1-6). However, these symptoms remain rare, and no cases of glomerular lesions have been reported to date.

To our knowledge, this is the first case report of focal segmental glomerulosclerosis (FSGS) due to renal microinfarction (renal ischemia) associated with Buerger's disease.

Case Report

A 43-year-old woman was admitted to our hospital with nephrotic-range proteinuria and renal dysfunction. She had no history of pregnancy. Although she had undergone a medical checkup each year, she had no history of hypertension until one year before the onset of nephrotic syndrome. She had first exhibited hypertension at a level of about 140-150/80-90 mmHg 1 year prior to admission at our facility but had not sought treatment because her home blood pressure was generally less than 140/90 mmHg. She developed sudden pain and necrosis in the second finger of the left hand four months prior to admission to our hospital (Fig. 1). A diagnosis of Buerger's disease was made based on the histological findings (Fig. 1c-e), the diagnostic criteria for thromboangitis obliterans (TAO), and Shionoya's clinical diagnostic criteria, which include: (i) an onset before 50 years old, (ii) a history of smoking, (iii) the presence of infrapopliteal arterial occlusions, (iv) either upper limb involvement or phlebitis migrans, and (v) the absence of atherosclerotic risk factors other than smoking (7, 8). This case satisfied items i, ii, iv and v from Shionoya's clinical diagnostic criteria, enabling us to exclude congenital diseases and collagen diseases such as systemic lupus erythematosus,

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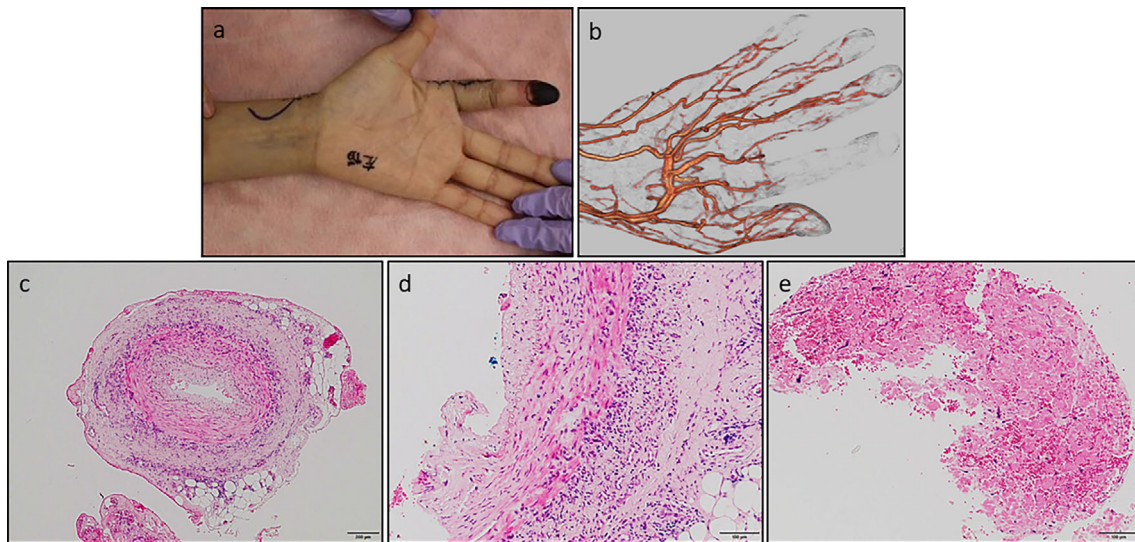
Figure 1. Imaging and histological findings of necrosis in the second finger of the left hand. (a) Necrosis in the second finger of the left hand. (b) Angiography of the left hand. (c) Vascular pathology observed via light microscopy [Hematoxylin and Eosin (H&E) staining]. (d) High-power field of the outer membrane wall (H&E staining). (e) Thrombus of the vascular lumen (H&E staining). Infiltration of inflammatory cells was observed in the outer membrane of blood vessels, and thrombus was observed in the lumen, consistent with Buerger's disease.

scleroderma, and Behcet's disease.

She received antismoking education, prostaglandin analog therapy, and hyperbaric oxygen therapy. However, these interventions had no effect, and she underwent vascular and free soft tissue transplant surgery. She had hypertension, with values of 150-170/80-100 mmHg at this time, and angiotensin II receptor blocker (ARB) treatment was started. However, she actually took the ARB only every third to seventh day, as her systolic blood pressure was frequently below 100 mmHg.

On admission, a urinalysis showed massive proteinuria (15 g/g creatinine), but urinary red blood cells were not seen. A blood examination revealed an elevated serum creatinine level of 1.07 mg/dL (estimated glomerular filtration rate, 45.2 mL/min/1.73 m^2) and a reduced serum albumin level of 2.8 g/dL. The complement 3 (C3) and total hemolytic complement (CH50) levels were within the normal ranges. Although antinuclear antibody was positive, autologous antibodies were negative. In addition, the patient had hypertension (179/122 mmHg) and showed high plasma renin activity (38.9 ng/mL/h) with a normal plasma aldosterone concentration (98.4 pg/mL) under intermittent ARB treatment (Table). A diagnosis of nephrotic syndrome was made according to proteinuria, hypoalbuminemia and hyperlipidemia. Among 27 glomeruli examined in the biopsy specimens, 9 showed global sclerosis, 4 showed segmental sclerosis with podocyte capping, 2 showed and tuft adhesion, 5 were collapsed, and 1 showed glomerular cystic formation (Fig. 2a-d). The tubulointerstitium showed mild involvement with interstitial fibrosis and tubular atrophy of about 20% of the cortex (Fig. 2e). No obvious infarction or thrombus was observed in the interlobular artery (Fig. 2f).

An immunofluorescence analysis showed nonspecific IgM deposition in the mesangium area. No dense deposits were detected via electron microscopy (Fig. 2g, h). These findings pathologically confirmed a diagnosis of FSGS not otherwise specified (NOS).

There were no findings that could explain the frequent secondary FSGS, such as drug use, viral infection, obesity (her body mass index was 16.6 kg/m^2), or a low birth weight. Although bilateral renal artery stenosis was not seen on renal artery ultrasound or magnetic resonance angiography (MRA) (Fig. 3a), a small focal renal infarction was seen on ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy (Fig. 3b). The patient had hypertension on admission, but this was diagnosed within one year prior to the diagnosis of Buerger's disease. Furthermore, there were no severe atherosclerotic changes and no risk factors for atherosclerosis other than smoking. Based on these findings, we diagnosed her with FSGS due to renal microinfarction associated with Buerger's disease. Thereafter, angiotensin-converting enzyme inhibitor (ACE-I) treatment was started; her hypertension immediately improved (100-120/70-80 mmHg), accompanied by the significant attenuation of proteinuria (1.5 g/g creatinine) (Fig. 4).

Discussion

Buerger's disease was first reported following the pathological examinations of 11 amputated limbs in 1908, with the disease described as inflammation of the arterial wall resulting in a cellular type of thrombosis (9). In some patients, it can be difficult to distinguish Buerger's disease from arteriosclerosis. In the present case, the patient presented with

Table. Laboratory Data at Admission.

| Urinalysis		Blood Chemistry		Immunology	
Gravity	1.02	TP	6.2 g/dL	CRP	0.03 mg/dL
pH	6	Alb	2.8 g/dL	IgG	1,284 (861-1,747) mg/dL
Protein	3+	AST	22 U/L	IgA	192 (93-393) mg/dL
	15.1 g/day	ALT	11 U/L	IgM	105 (50-269) mg/dL
Blood	-	LDH	160 U/L	C3	103 (73-138) mg/dL
β2MG	11,361 (<200) μg/L	T-cho	307 mg/dL	C4	27 (11-31) mg/dL
NAG	39.8 (<11.5) U/L	LDL-C	172 mg/dL	CH50	56 (31.6-57.6) U/mL
		TG	158 mg/dL	Antinuclear antibody	
Blood cell count		BUN	17.3 mg/dL	Homogenous	1:640 titer
WBC	7,910 /μL	Cre	1.07 mg/dL	Discrete speckled	1:640 titer
Hb	10.3 g/dL	e-GFR	45.2 mL/min/1.73m^2	Anti-ssDNA antibody	19 (<25) IU/mL
Plt	48×10^4 /μL	UA	7.4 mg/dL	Anti-dsDNA antibody	1.2 (<12) AU/mL
		Na	138 mEq/L	Anti-RNP antibody	0.3 (<10) U/mL
Viral Markers		K	4.0 mEq/L	Anti-Sm antibody	0.2 (<10) U/mL
HBs-Ag	-	Cl	102 mEq/L	Anti-centromere antibody	8.1 (<10) U/mL
HBs-Ab	-	Ca	8.6 mg/dL	Anti-SS-A antibody	0.3 (<10) U/mL
HCV-Ab	-	P	4.0 mg/dL	Anti-SS-B antibody	1 (<10) U/mL
HIV-Ab	-	PRA	38.9 (0.20-3.90) ng/mL/h	Anti-Scl-70 antibody	0.9 (<10) U/mL
		PAC	98.4 (35.7-240) pg/mL	Anti-Jo-1 antibody	0.1 (<10) U/mL
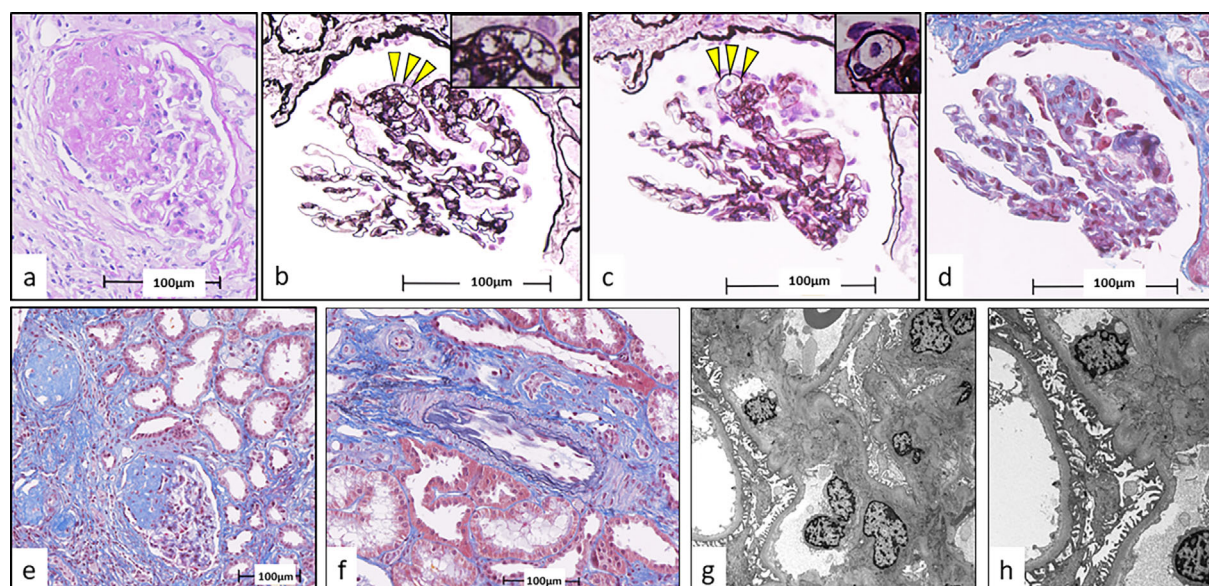
Figure 2. Light and electron microscopy showing focal segmental glomerulosclerosis. (a) Periodic-acid Schiff (PAS) staining (bar=100 μm). (b, c) Periodic-acid methenamine (PAM) staining (bar=100 μm). (d, e) Masson's trichrome (MT) staining (bar=100 μm). (f) Masson's trichrome (MT) staining of the interlobular artery (bar=100 μm). (g) Electron microscopic findings. (h) High-power field of electron microscopic findings. These findings indicated focal segmental glomerulosclerosis lesions not otherwise specified (NOS) with foam cells (b, c; thick arrow and high magnification). The tubulointerstitium showed mild involvement with interstitial fibrosis and tubular atrophy of about 20% of the cortex (e). No obvious infarction, thrombi, or severe atherosclerotic changes were found in the interlobular artery. (f) No dense deposits were detected via electron microscopy (g, h).

hypertension on admission; however, this condition had been first diagnosed less than 1 year earlier, and her home blood pressure level had been under 140/90 mmHg until the diagnosis of Buerger's disease. Furthermore, no severe atherosclerotic changes were revealed by a kidney biopsy, there were no risk factors for atherosclerosis other than smoking,

and the patient was a woman under 50 years old, which satisfied 4 out of 5 items from Shionoya's clinical diagnostic criteria. Therefore, the patient was diagnosed with Buerger's disease.

This case exhibited nephrotic-range proteinuria and renal dysfunction, and a kidney biopsy revealed an FSGS lesion.
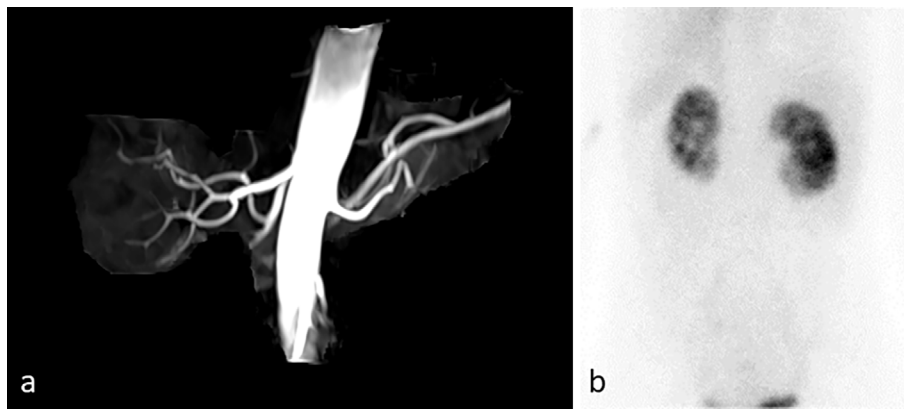
Figure 3. Imaging findings suggesting renal ischemia. (a) Magnetic resonance angiography (MRA). (b) ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy. Although bilateral renal artery stenosis was not seen on MRA (a), a small focal renal infarction was seen on ^{99m}Tc-DMSA renal scintigraphy (b), suggesting focal renal infarction.
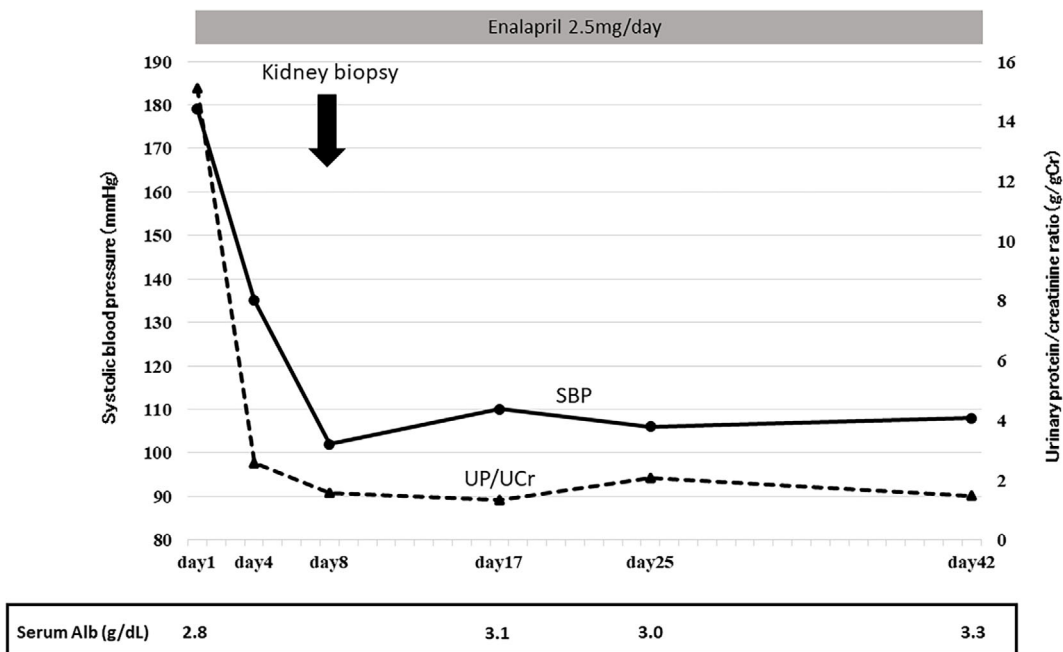

Figure 4. Clinical course over the duration of the hospitalization. After commencement of angiotensin-converting enzyme inhibitor therapy, hypertension immediately improved, along with significant attenuation of proteinuria.

This is the first case of histologically proven glomerular lesions in Buerger's disease.

FSGS is caused by a wide variety of renal diseases. It is defined as a clinicopathological syndrome manifesting with proteinuria, usually within the nephrotic range, and is associated with focal and segmental glomerular lesions and podocyte foot process effacement. Primary FSGS must be differentiated from secondary forms, including those arising from mutations in genes encoding podocyte-associated proteins, viruses, drug toxicity, and structural-functional adaptations mediated by processes such as intrarenal vasodilation, increased glomerular capillary pressure and impaired plasma flow among other maladaptive processes (10). Although we could not exclude mutations in genes encoding podocyte-

associated proteins, the patient had no findings associated with frequent secondary FSGS, such as viral infection, drug toxicity, obesity, or a low birth weight.

Renal ischemia is a possible cause of FSGS, although the mechanisms remain unclear. In a review article, Meyrier et al. discussed two opposing mechanisms. In cases of ischemia within a collapsed glomerular tuft, which may undermine podocyte viability and/or anchorage to the glomerular basement membrane, renal ischemia may lead to marked vasoconstriction of the glomerular efferent arterioles and tuft expansion, which exerts traction force on podocytes (11). We found no obvious infarction or thrombus at the interlobular artery level in the kidney biopsy specimen. Previous studies have found that renal infarction associated with

Buerger's disease can be visualized via contrast computed tomography (CT) or magnetic resonance imaging (MRI) (1-3), but in this case, it was not visualized via MRA. Although we did not observe renal infarction or thrombus at the interlobular artery level in the renal biopsy specimen, mottled defects were seen on ^{99m}Tc-DMSA renal scintigraphy, suggesting small focal renal infarctions. We were unable to confirm any potential cause of FSGS other than renal ischemia. We suspect that, in this case, the FSGS was caused by micro renal infarctions (smaller than several millimeters but larger than several dozen to hundreds of micrometers) associated with Buerger's disease.

Another potential mechanism involves the generation of large amounts of angiotensin II by the ischemic kidney, which may promote the induction of podocyte changes and FSGS (12). Our patient had been treated intermittently with an ARB, depending on the blood pressure. Treatment-related outcomes included a markedly high plasma renin activity (38.9 ng/mL/h) and a normal plasma aldosterone concentration (98.4 pg/mL), suggesting that the intrarenal angiotensin II levels were very high.

Therefore, we postulated that vasoconstriction of the glomerular efferent arterioles in association with Buerger's disease and/or elevated intrarenal angiotensin II might result in glomerular hyperfiltration followed by pressure natriuresis, massive proteinuria, and FSGS. Nitric oxide (NO) synthesis is necessary for hyperfiltration (13), so we used an ACE-I rather than an angiotensin II type 1 receptor blocker. After commencement of ACE-I therapy, hypertension improved immediately (100-120/70-80 mmHg); proteinuria also improved (1.5 g/g creatinine), supporting our diagnosis.

Malignant hypertension is a cause of secondary FSGS (14). Nagata et al. reported that secondary FSGS could occur due to renovascular hypertension, even if the duration of hypertension was short (15). Therefore, we were unable to exclude the possibility that the development of the FSGS lesion in this case might have been caused by microvascular hypertension due to Buerger's disease. As the patient's blood pressure did not reach the level of malignant hypertension throughout the observation period and improved immediately with a small amount of ACE-I therapy, we concluded that this was a case of secondary FSGS due to renal microinfarction (renal ischemia) associated with Buerger's disease.

Informed consent was obtained from all participants in the study.

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