CASE REPORT

Complex glomerular pathology of thrombotic microangiopathy and focal segmental glomerulosclerosis forms tumor-like mass in a renal transplant donor with severe renovascular hypertension

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Abstract The pathogenesis of glomerular hypertension-mediated FSGS and its histological variations in humans remains unknown. A 47-year-old man developed nephrotic syndrome, renal dysfunction, and malignant hypertension 2 years after donating a kidney to his son. The donor's remnant kidney developed renal mass at an upper pole which was fed by an aberrant artery that branched from the root of the renal artery. Furthermore, the main non-aberrant renal artery demonstrated severe stenosis that caused renovascular hypertension, resulting in malignant hypertension. Upon radiological examinations, a tumorous mass was detected. Because of progressive renal dysfunction, nephrectomy was performed. The kidney revealed a diffuse distribution of complex FSGS lesions, i.e., a random combination of cellular/collapsing FSGS and glomerular thrombotic microangiopathy, confined to the renal mass, whereas such lesions were absent in the non-mass portion. This indicated that severe glomerular hypertension alone caused FSGS with TMA features. Heterogeneous FSGS lesions let us surmise that glomerular hypertension promoted simultaneous damages in endothelial cells and

podocytes, which synergistically progressed to glomerulosclerosis. This unique case uncovers causal relationships between unusual glomerular hypertension and severe forms of FSGS that was possibly caused by the disruption of homeostasis sustained by podocytes and endothelial cells.

Keywords Renovascular hypertension · Donor kidney · Renal mass · Nephrotic syndrome · Focal segmental glomerulosclerosis

Introduction

Focal segmental glomerulosclerosis (FSGS) is a progressive kidney disease characterized by focal and scattered distribution of segmental glomerulosclerosis [1]. FSGS is often associated with a variety of conditions; however, causal relationships between each condition and FSGS are merely speculative, and pathogenesis is difficult to demonstrate.

Hypertension is one of the major causes of FSGS [2, 3]. Previous reports of hypertension-associated FSGS were generally of classic types (matrices accumulation and hyalinosis), corresponding to NOS or the perihilar variant of the Columbia classification [4, 5]. Histological phenotypes of FSGS may depend on the levels and duration of hypertension, and marked hypertension showed scattered distribution of NOS or cellular variant [6–8]. However, causal relationships between hypertension and histological phenotypes of FSGS and its pathophysiology are unknown.

We present a case of a kidney donor developed severe systemic hypertension, nephrotic syndrome and progressive renal dysfunction 2 years after the donation. Radiology demonstrated renal mass in the donor's remaining kidney that histologically showed a diffuse distribution of

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Fig. 1 Gross morphology and histology of the renal mass. **a** Angiographic image of the left kidney prior to the kidney donation showing two renal arteries branched from the aorta; the superior aberrant artery (arrow head) that branched from the root of main renal artery supplies the upper portion of the left kidney. No stenosis in the main arteries (arrow). **b** 3D-angiography reveals aberrant artery (arrow head) branching from the root of the main renal artery. **c** Enhanced MRI of the donor's remnant kidney at nephrectomy. Note renal mass (arrow heads) occupying a half of the upper pole slice of the kidney (arrow heads). **d** Nephrectomy material shows well-demarcated (arrow heads) tumor mass without capsule in the upper pole. **e** Cut surface shows pale cortex with thickening, which is a main component of the mass. Note that no capsule and renal pyramid are preserved. **f** Histology at the border of mass and surroundings. Mass part (left side) shows diffuse glomerular enlargement and tubular dilatation which occasionally shows cystic dilatation containing protein casts. Such lesions are absent just next to the mass (right side). Dashed line indicates border line. **g** Aberrant artery supplying the mass shows substantial thickening in the media (arrow), and is associated with diffuse, marked dilatation and hypertrophy in the tubuli. **h** Larger magnification of mass part reveals diffuse endocapillary, mesangial, and extra-capillary hypercellularity with overlying epithelial hyperplasia. **i** In contrast, glomeruli of the non-mass part reveal some capillary collapse. All scale bars indicate 100 μ m

complex FSGS and TMA lesions. The present case suggested the pathogenesis and histological variations of progressive FSGS caused by excessive glomerular hypertension.

Case report

Clinical history and initial laboratory data

A 47-year-old Japanese male donated his right kidney to his son who had end stage renal disease of unknown cause. Medical examinations of the father before the kidney donation showed no proteinuria and hypertension, and he was cleared by our standard protocol for kidney donation. Preoperative angiography demonstrated two renal arteries supplying the left kidney; one was in a usual position that showed no stenosis, and the other was an aberrant artery that branched from the root of main renal artery and supplied the upper pole (Fig. 1a, b). After donation of the right kidney, the remaining kidney function was stable [serum creatinine (sCr) 1.0 mg/dl]. However, 2 years after the donation, he complained of severe headaches. At that time, he showed severe hypertension (220/130 mmHg), renal dysfunction (sCr 1.25 mg/dl), and mild proteinuria. Five months later, he was hospitalized because of vomiting and abdominal pain. His blood pressure was 162/82 mmHg, but sCr was 6.8 mg/dl. Urinalysis revealed 4.7 g/day of proteinuria with microhematuria. Although plasma renin activity and aldosterone concentration were not examined, other laboratory data did not show any systemic diseases.

Computed tomography showed ca. 6 cm of solid mass at the upper portion of the kidney. The mass was only weakly enhanced on a magnetic resonance scan with administration of gadolinium-labeled diethylenetriaminepentaacetic acid (Fig. 1c). Radiological data suggested renal tumor. Because severe general symptom and proteinuria were likely caused by kidney-driven severe hypertension and malignant tumor was not excluded, nephrectomy was performed after intimate informed consent. After nephrectomy, he received hemodialysis and his blood pressure rapidly decreased. The recipient did not have any clinical symptoms and shows stable renal function without proteinuria 12 years after transplantation.

Nephrectomized tissue revealed a solitary mass-like lesion (6.2 $\times$ 3.3 cm) at the upper portion (Fig. 1d). The main artery showed severe luminal stenosis at the downstream of branching, which was not found before transplantation by angiography. The aberrant artery supplied the upper portion of the kidney where a mass developed. A cut surface revealed that the mass was thickened cortex and the corticomedullary junction was identified (Fig. 1e). Histologically, the demarcation between the mass and neighboring cortex was well identified, despite no capsule (Fig. 1f). The aberrant artery supplying the mass showed wall thickening by vascular smooth muscle cells hyperplasia (Fig. 1g). The mass was composed of diffuse tubular hypertrophy with a diffuse distribution of complex glomerular lesions reminiscent of FSGS and TMA in more than 90 % of glomeruli (Fig. 1h), whereas the non-mass part showed diffuse glomerular collapse without such lesions (Fig. 1i). The complex FSGS lesions included massive hyaline degeneration in podocytes, parietal cell hyperplasia, intracapillary foam cells accumulation, glomerular TMA, and mesangial hyperplasia (Fig. 2). Serial sections using immunohistochemistry showed that epithelial hyperplasia was virtually podocalyxin-negative (monoclonal anti-podocalyxin antibody kindly provided by Dr. Atkins) instead expressed claudin-1 virtually (rabbit polyclonal antibody, Zymed Laboratories, USA) indicating parietal cell origin. Immunofluorescent microscopy showed no distinct immunoglobulin and complement deposition. Endothelial hypercellularity, swelling, and occasional thrombus formation were seen in the arterioles close to the glomeruli. No distinct lesion suggesting TMA is noted in upstream of arterioles.

Discussion

The present case provides intriguing clues to elucidate the pathogenesis of hypertension-mediated FSGS in humans.

The pioneer works by Bohle et al. and others have shown an association of FSGS with systemic hypertension;

Fig. 2 Complex glomerular features in mass portion. **a** Two glomeruli similarly show marked tuft collapse, but one shows a large cellular crescent (*arrow*) and the other shows massive hyaline degeneration in podocytes (*arrow head*). **b** Global hypercellularity mimicking mesangial sclerosis with nodule formation (*arrow head*). **c** Segmental intracapillary hypercellularity is associated with epithelial hyperplasia, swelling, and degeneration (*arrow head*). Note that the left half portion was free from such lesions. **d** Global intra- and extra-capillary hypercellularity with double contour showing TMA-like lesion. **e** Intracapillary thrombus formation (*arrow heads*) is associated with massive epithelial hyaline degeneration. **f** Glomerulus with cellular FSGS lesion represents intracapillary foam cells accumulation at the tip domain (*arrow head*). Serial sections of FSGS lesion stained by anti-podocalyxin antibody (**g**) and anti claudin-1 antibody (**h**). Focal loss of podocalyxin staining is replaced by claudin-1 expressing cells. Note that these two protein expressions reveal a nearly complete mirror image pattern. **i** Vascular pole beneath the FSGS lesion reveals polar vasculosis with hyaline deposition (*arrow heads*). **j** Afferent artery near the complex glomerular lesions shows endothelial hyperplasia and swelling (*arrow*) and thrombi (*arrow head*) that occlude lumina. All scale bars indicate 100 μ m

however, the mechanism by which FSGS lesion developed is insufficiently understood [9]. Decompensated nephrosclerosis is a known basis of secondary FSGS that demonstrates mixed lesions of ischemic glomerulosclerosis and classic type of segmental sclerosis, such as NOS or perihilar sclerosis [10–12].

The present case showed severe hypertension, rapid renal dysfunction, and nephrotic syndrome in the remnant kidney 2 years after the kidney donation. At nephrectomy, the main renal artery feeding the majority of the renal parenchyma was found to be stenosed at the downstream of branching of aberrant renal artery. Although the plasma renin activity was not measured, the improvement of hypertension shortly after nephrectomy suggested that renovascular hypertension (RVH) was the cause of the severe hypertension. Diffuse glomerular collapse corresponding to the stenotic main artery indicated hypoperfusion-mediated progressive renal dysfunction. Previously published RVH reports revealed heavy proteinuria, and FSGS was found in the contralateral kidneys showing scattered distribution of NOS variant [7, 13–15]. In our case, the patient's remaining kidney had two different kidney compartments supplied by independent renal arteries. Previously reported FSGS with malignant hypertension showed a scattered distribution of NOS or cellular variant [6, 8]. Complex phenotypes of malignant FSGS lesions in our case were possibly because of RVH that targeted a small kidney compartment via an aberrant artery.

FSGS is recognized as a podocyte disease; however, intracapillary hypercellularity, and mesangial changes are occasionally observed [1, 16]. The basic features identifying a FSGS lesion are intracapillary alterations with overlying visceral epithelial damage that occurs in a segmental manner [17]. Numerous FSGS glomeruli (250

glomeruli/section) in the mass from this case provided unique opportunity to observe the histological variation of FSGS by a single cause, severe glomerular hypertension. As shown in Fig. 2, FSGS lesions include a random combination of massive hyaline degeneration in podocyte and parietal cells hyperplasia as labeled by claudin-1, and intracapillary thrombi and hypercellularity often contain foam cells. These complex FSGS lesions are unlikely to be explained by podocyte injury alone, and interactions between podocytes and endothelial cells may underlie the pathogenesis of marked glomerular hypertension-mediated FSGS.

The majority of FSGS lesions in this case were global and complex, but some revealed early/incipient lesions, which may explain the sequential development of FSGS in this condition. Glomerular hypertension may attack both endothelial cells and podocytes. Early/incipient lesions include segmental occurrence of intra- and extra-capillary hypercellularity or global or segmental podocyte degeneration with underlying tuft collapse. In experimental studies, glomerular TMA and podocyte injury were associated with severe hypertension/hyperfiltration, such as 5/6 nephrectomy or DOCA-hypertensive models, whereas moderate hypertension/hyperperfusion models revealed podocyte injury alone [18–20]. The development of glomerular TMA may need higher blood pressure than that of podocytes and heterogeneous pressure gradient among the glomerular tuft may result in complex FSGS lesions.

These biphasic glomerular alterations of intra- and extra-capillary abnormalities may not develop independently. Cancer patients treated by anti-vascular endothelial growth factor antibody (VEGF) and mice with podocyte selective VEGF deletion resulted in TMA and mesangiolysis/proliferation [21]. Podocyte selective toxin models in mice caused glomerular TMA that progressed to collapsing FSGS [20]. These findings indicated that podocyte injury caused TMA by decreasing podocyte-derived VEGF and histological transfiguration between TMA and FSGS. The disruption of local podocyte endothelial cell crosstalk presumably was the basis of the segmental nature of FSGS.

Recent experimental studies showed the mechanism of intra- and extra-capillary interactions during podocyte injury, leading to FSGS. Fulminate podocyte injury models are associated with parietal cell hyperplasia by aberrant Notch1 induction, and the upregulation of endothelial plasminogen activator inhibitor type 1 promoted further podocyte damages by disrupting the podocyte integrin anchoring [22, 23]. Progressive podocyte loss under hyperlipidemia promoted local lipid peroxidation and endothelial cell injury, resulting in the upregulation of adhesion molecules that synergistically promoted macrophage entrapment and transformation to foam cells [24]. From these findings, we speculated the variation of FSGS

morphology in this case as the disruption of podocytes and endothelial cell crosstalk caused by severe mechanical stress on the filtration barrier.

In conclusion, the present unusual case indicated causal relationships between extreme glomerular hypertension and the unique histology of FSGS. In addition, various glomerular features suggested the morphogenesis of hypertension-mediated FSGS as disruption of podocyte endothelial cell crosstalk in humans.

Compliance with ethical standards

Conflict of interest The authors declare that they have no relevant financial interests.

Human and animal right This article is principally based on the observation and does not contain any studies with human participants performed by any of the authors.

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