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CASE REPORT

A case of hypertensive emergency with alveolar hemorrhage and thrombotic microangiopathy

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Abstract

A 28-year-old woman with a 5-year history of untreated hypertension was admitted for respiratory distress, hemoptysis, and retinopathy. Computed tomography showed diffuse plaques in both lung fields. Acute kidney injury, hemolytic anemia, and thrombocytopenia were noted. Kidney biopsy showed thrombosis with fibrinoid necrosis and edematous intimal thickening and luminal narrowing of the small renal artery, indicating thrombotic microangiopathy; the majority of glomeruli were collapsed. After 8 weeks of treatment with antihypertensive drugs, serum creatinine decreased to 1.0 mg/dL, and the patient recovered. In the absence of any other underlying disease, malignant nephrosclerosis associated with a hypertensive emergency was diagnosed.

Keywords Thrombotic microangiopathy · Malignant hypertension · Malignant nephrosclerosis · Hemolytic uremic syndrome

Abbreviations

CT	Computed tomography
HUS	Hemolytic uremic syndrome
TMA	Thrombotic microangiopathy

Introduction

Before the widespread availability of antihypertensive drugs, patients with severely elevated blood pressure and encephalopathy, retinopathy, or acute kidney injury had a poor prognosis and were thus given a diagnosis of malignant hypertension. However, advances in treatments for hypertension led to a dramatic decrease in the number of such cases, and the diagnoses hypertensive emergencies (or urgencies) and accelerated hypertension were introduced as alternatives to malignant hypertension [1].

Nonaka et al. examined the clinical presentation and renal pathology of 12 patients with hypertensive emergencies in the form of hypertensive emergency-related nephropathy and reported that so-called onion skinning of small renal arteries was characteristic and fibrinoid necrosis was rare [2]; however, many textbooks describe fibrinoid necrosis as a characteristic finding of this disease [3, 4].

Here, we present a case of hypertensive emergency with a finding of hemolytic uremic syndrome (HUS) in a 28-year-old female patient. We discuss the clinical and renal pathology of the disease and reconsider the disease characteristics.

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Case report

A 28-year-old woman was admitted to the emergency to our hospital because of bloody sputum and dyspnea. One week before admission, she had noticed decreased vision and fatigue. She had been diagnosed with hypertension (170/90 mmHg) at the age of 23 years, but had refused treatment.

On admission, the patient was 150 cm tall and weighed 48.0 kg. Her blood pressure was 233/125 mmHg; heart rate, 110 beats/min; and temperature, 36.8 °C. Heart sounds were normal, but coarse crackles were heard bilaterally in the chest. Edema was present in the lower extremities. The complete blood count was as follows: erythrocytes, 27.7×10^6/μL; hemoglobin, 7.0 g/dL; leucocytes, 19,570/μL; and thrombocytes, 13.1×10^4/μL. The results of blood chemistry tests were as follows: serum albumin, 3.8 g/dL; serum creatinine, 6.2 mg/dL; lactate dehydrogenase, 1644 U/L; C-reactive protein, 1.0 mg/dL, and haptoglobin, 0 mg/dL (reference range, 80–200 mg/dL). Urine analysis was not possible because of anuria. Computed tomography (CT) showed extensive mottled shadows in both lung fields (Fig. 1), but no renal atrophy or hydronephrosis.

The rapid development of renal failure with alveolar hemorrhage suggested anti-neutrophil cytoplasmic antibody (ANCA)-related microscopic polyangiitis or anti-glomerular basement membrane (anti-GBM) disease. Therefore, steroid pulse therapy with methylprednisolone (0.5 g/day) for 3 days and hemodialysis combined with double-filtration plasmapheresis therapy were started. These treatments improved the patient's respiratory distress. However, MPO/PR3-ANCA and serum GBM antibody tests were negative, so ANCA-related microscopic polyangiitis and anti-GBM disease were ruled out. P and C ANCA measured using an indirect fluorescent antibody technique were also negative.

Subsequently, HUS was diagnosed because of acute renal injury, hemolytic anemia, and thrombocytopenia; however, the underlying diseases that can cause HUS were ruled out

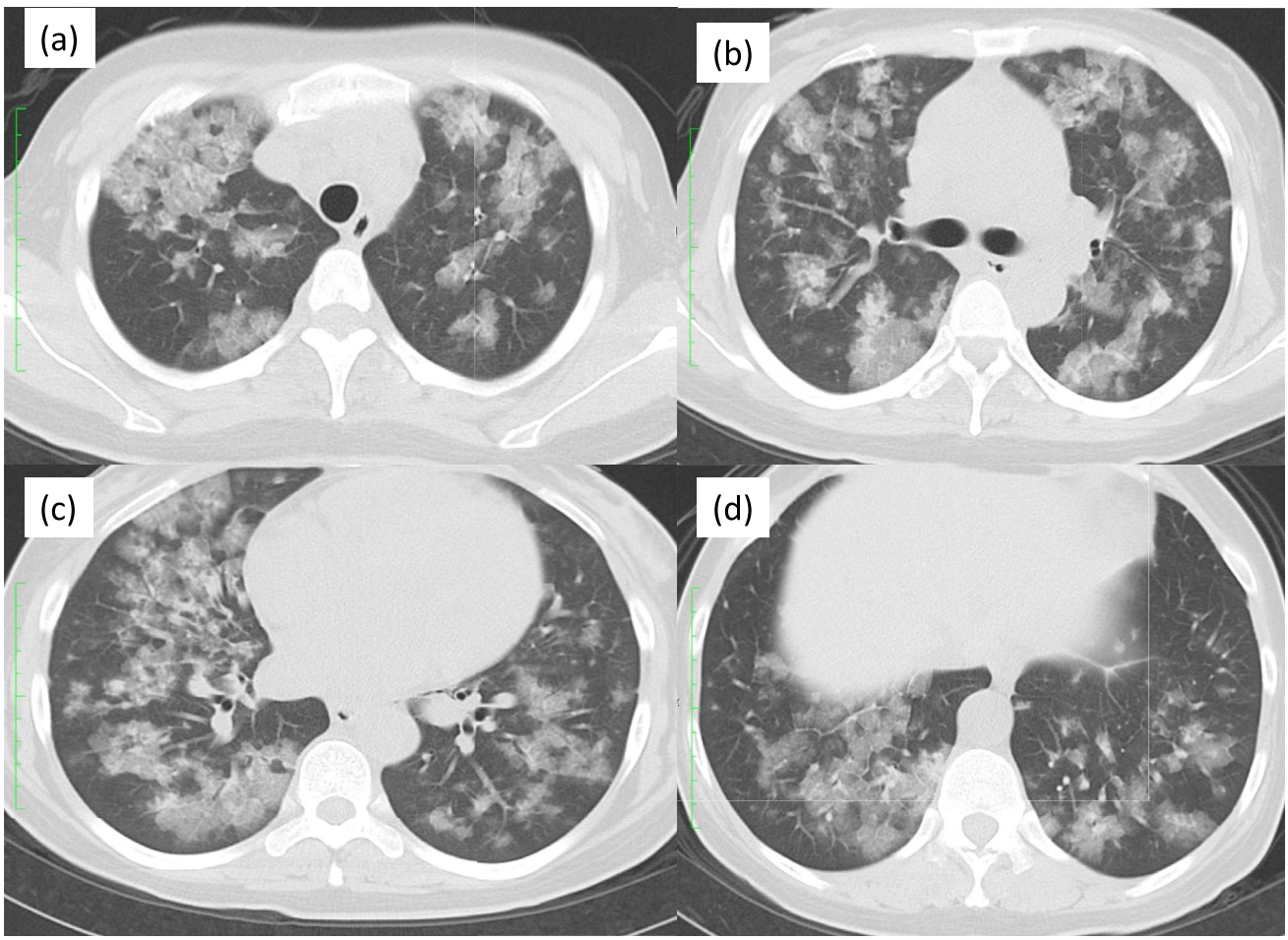

Fig. 1 Computed tomography findings. Extensive mottled shadows were observed throughout both lung fields. **a** Lung fields of the upper lobe; **b** lung fields of the upper middle lobe; **c** lung fields of the lower middle lobe; **d** lung fields of the lower lobe

because the tests for a disintegrin-like metallopeptidase with thrombospondin type 1 motif 13 activity and autoantibodies, including antinuclear antibody, double-strand DNA antibody, and antiphospholipid antibody, were negative.

Because of the negative results of the above tests, the patient was diagnosed with a hypertensive emergency or malignant hypertension because of the presence of severe hypertension; advanced retinopathy lesions, including macular edema and fundus hemorrhage; and hyperreninemia, with renin activity greater than 20.0 ng/mL/h (reference range, 0.2–2.9 ng/mL/h).

Echocardiography showed left ventricular hypertrophy with an interventricular septal thickness of 15 mm (reference range, < 8 mm), left ventricular posterior wall thickness of 14 mm (reference range, < 8 mm), and left ventricular (LV) mass of 304 g (reference range, 66–150 g).

Five days after admission when it was confirmed that hypertension was controlled within the reference range, a kidney biopsy was performed to determine the cause of renal failure.

Kidney biopsy

At kidney biopsy, five specimens were obtained. On light microscopy, the tubulointerstitium showed extensive blue color on Masson trichrome staining (Fig. 2a), suggesting a markedly ischemic change, although global sclerosis was present in only 1 out of 28 glomeruli. Most of the glomeruli were collapsed, and narrowing and occlusion of the small renal arteries with edematous changes in the intima were observed (Fig. 2b, c). Thrombus formation with fibrinoid necrosis extending from the interlobular artery to the glomerular pole was characteristic (Fig. 2d), and fibrin deposits were seen in three glomeruli (Fig. 2e). Thrombus formation with fibrinoid necrosis and numerous erythrocytes was also observed in the glomerular capillaries (Fig. 2f, g). In addition to endothelial cell swelling with mesangiolysis (Fig. 2h), hyperplasia of enlarged epithelial cells with hyaline droplets (Fig. 2i), extensive tubular necrosis with flattening of tubular epithelial cells (Fig. 2j), and hyaline drop degeneration of the tubular epithelium (Fig. 2k) were noted.

Immunofluorescence showed no significant deposition of immunoglobulin G (IgG), IgA, IgM, C3, or C1q. Electron microscopy showed subendothelial edema and endothelial and epithelial cell enlargement (Fig. 2l). Endothelial cell fenestration disorder was also seen (Fig. 2m).

Since atypical hemolytic uremic syndrome (aHUS) was suspected in the differential diagnosis of this patient, causative gene analysis for aHUS including CFH, CFI, CD46, C3, CFB, THBD, and DGKE was performed, and all negative data were confirmed.

Because of the findings of thrombotic microangiopathy (TMA) with fibrinoid necrosis and acute tubular necrosis, the patient was diagnosed with malignant nephrosclerosis due to a hypertensive emergency.

Clinical course

After the patient was diagnosed on the basis of the kidney biopsy findings, double-filtration plasmapheresis therapy and steroid therapy were discontinued, and the patient was switched to antihypertensive treatment with an angiotensin II receptor blocker (losartan) in addition to a calcium channel blocker (amlodipine) and an α/β antagonist (carvedilol). Two weeks later, urination gradually increased. After 3 weeks, the patient discontinued hemodialysis. After 8 weeks, serum creatinine improved to 1.1 mg/dL (Fig. 3). Ten year later, at the time of writing this manuscript, the patient continues to take the antihypertensive medications and her blood pressure and creatinine level (0.8 mg/dL) are normal.

Discussion

We experienced a case of malignant hypertension and hypertensive emergency with renal pathology of malignant nephrosclerosis. Malignant hypertension is one of the primary causes of hypertensive renovascular disease and is diagnosed after exclusion of the secondary component of hypertensive renovascular disease [5]. The glomerular lesions of malignant hypertension are characterized by ischemic retraction of glomeruli, and the small artery lesions are characterized by mucoid intimal change, concentric medial smooth muscle hypertrophy, endothelial swelling (together referred to as onion skinning), fibrinoid necrosis, and fibrin thrombi; however, little information is available on the clinical presentation of the disease [5].

We performed a PubMed search for publications on this disease and identified only one article that reported on both the clinical and the renal pathology: Nonaka et al. [2] found that the mean age of patients with hypertensive emergency-related nephropathy was 40 years and that most of them were male. The patients had been diagnosed with hypertension at a young age, but had no history of subsequent hospital visits. The mean value of serum creatinine was 6.1 mg/dL, and renal function was improved by antihypertensive treatment but did not normalize. When hospital visits were interrupted, the renal insufficiency worsened again. Hyperreninemia and hyperaldosteronism were present. The patients were in renal failure, but did not have hyperkalemia because hyperaldosteronism caused metabolic alkalosis. Patients had evidence of left ventricular hypertrophy, reflecting a long history of untreated hypertension, and patients with end-stage renal

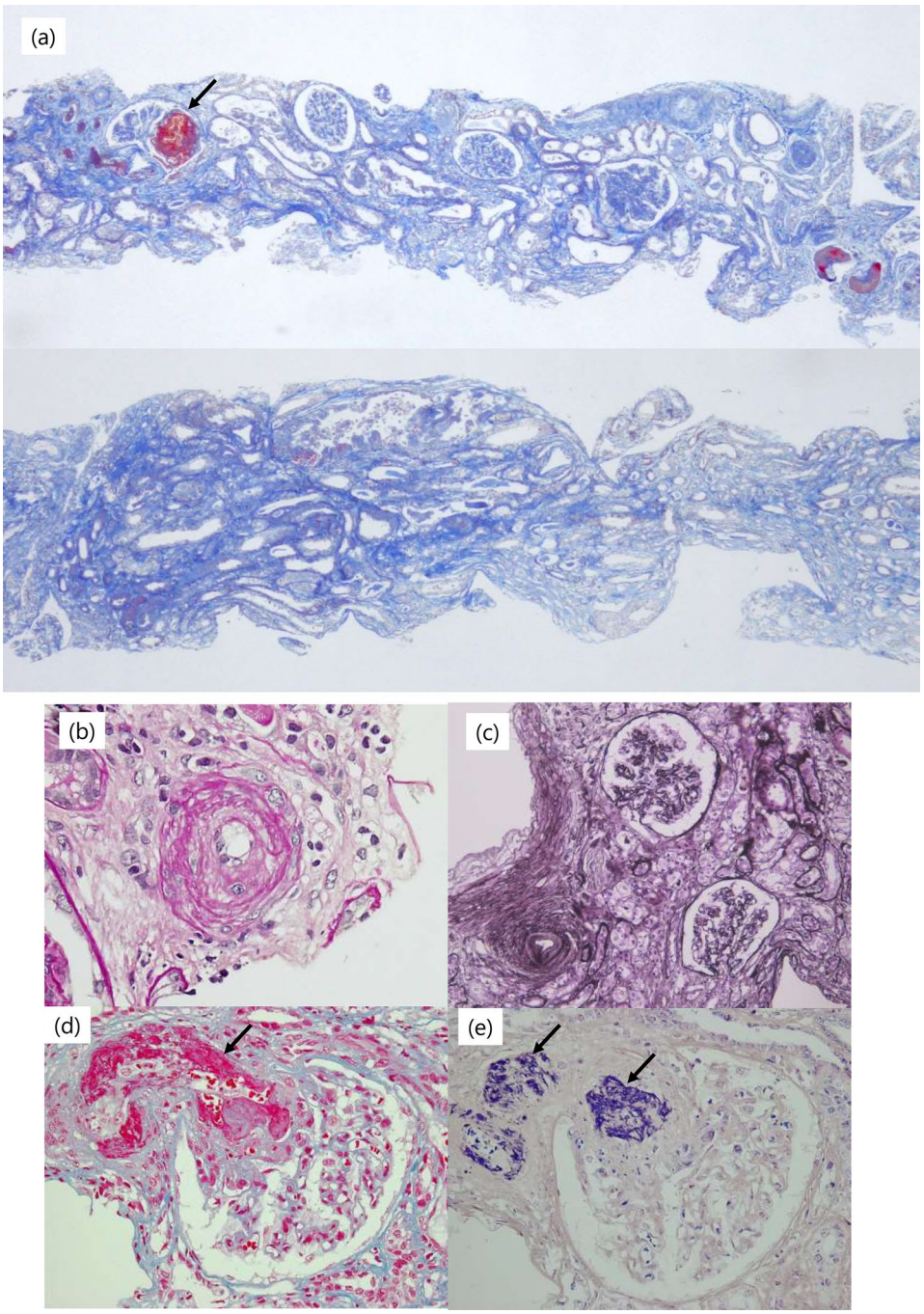

Fig. 2 Kidney biopsy findings. **a** The tubulointerstitium showed extensive blue color on Masson trichrome staining, suggesting a strong ischemic change. Fibrinoid necrosis (arrow) was seen in three glomeruli (original magnification ×60). **b** Narrowing and occlusion of the arterioles were observed, with edematous changes in the intima (periodic acid Schiff staining; original magnification ×400). **c** Most of the glomeruli were collapsed, and narrowing and occlusion of the interlobular artery were observed. Periodic acid methenamine silver staining (original magnification ×200). **d** Thrombus formation with fibrinoid necrosis (arrow) extending from the interlobular artery to the glomerular pole was characteristic (Masson trichrome staining; original magnification ×200). **e**: Fibrin deposits (arrow) were observed (phosphotungstic acid hematoxylin staining; original magnification ×200). **f** and **g** Thrombus formation with fibrinoid necrosis with numerous erythrocytes (arrow) was also observed in the glomerular capillaries with Masson trichrome staining (**f**, original magnification ×400) and periodic acid methenamine silver and Masson trichrome staining (**g**, original magnification ×400). **h** Endothelial cell swelling with mesangiolysis (arrow) was observed (periodic acid methenamine silver staining; original magnification ×400). **i** Hyperplasia of enlarged epithelial cells with hyaline droplets (arrow) was observed (periodic acid Schiff staining; original magnification ×400). **j** Extensive tubular necrosis with flattening of tubular epithelial cells (arrow) was observed (hematoxylin and eosin staining; original magnification ×200). **k** Hyaline drop degeneration (arrow) of the tubular epithelium was observed (hematoxylin and eosin staining; original magnification ×200). **l** Electron microscopy showed subendothelial edema and both endothelial cell enlargement (large arrow) and epithelial cell enlargement (small arrow). **m** Endothelial cell windowing disorder (arrow) was also seen

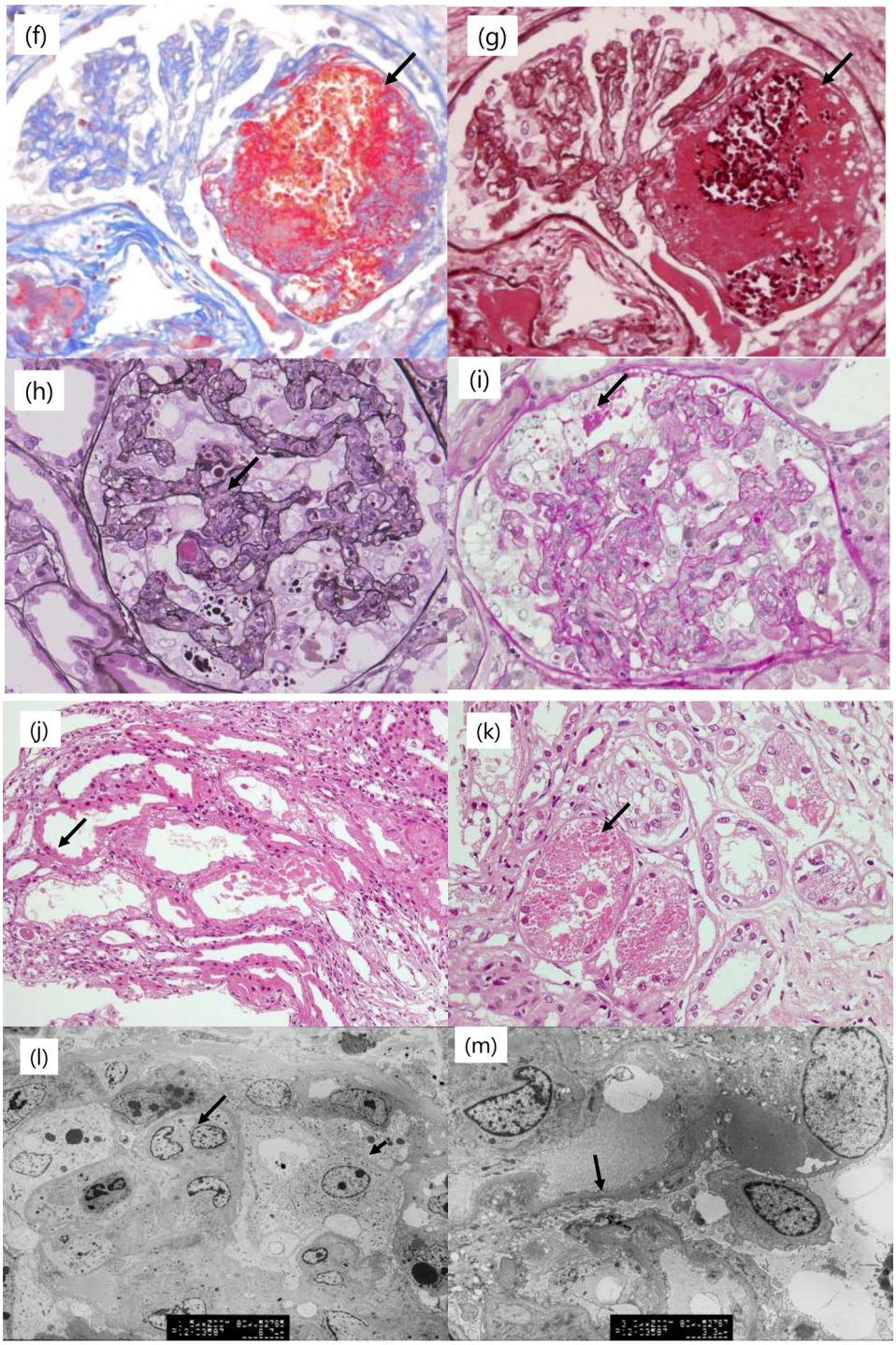

Fig. 2 (continued)

failure were characterized by clinical symptoms corresponding to HUS. Kidney biopsy showed edematous thickening of the intima of the small renal arteries and luminal stenosis, i.e., onion skinning, and many collapsed glomeruli. A small area of fibrinoid necrosis was found in only 1 out of the 12 patients [2].

We searched PubMed to investigate whether other diseases besides malignant hypertension show onion skinning of the small renal artery and/or glomerular TMA lesions, and found that similar lesions were reported in patients with the following underlying diseases: familial Mediterranean fever [6], lupus nephritis [7], antiphospholipid syndrome nephropathy [8, 9], scleroderma renal crisis [10], polymyositis [11,

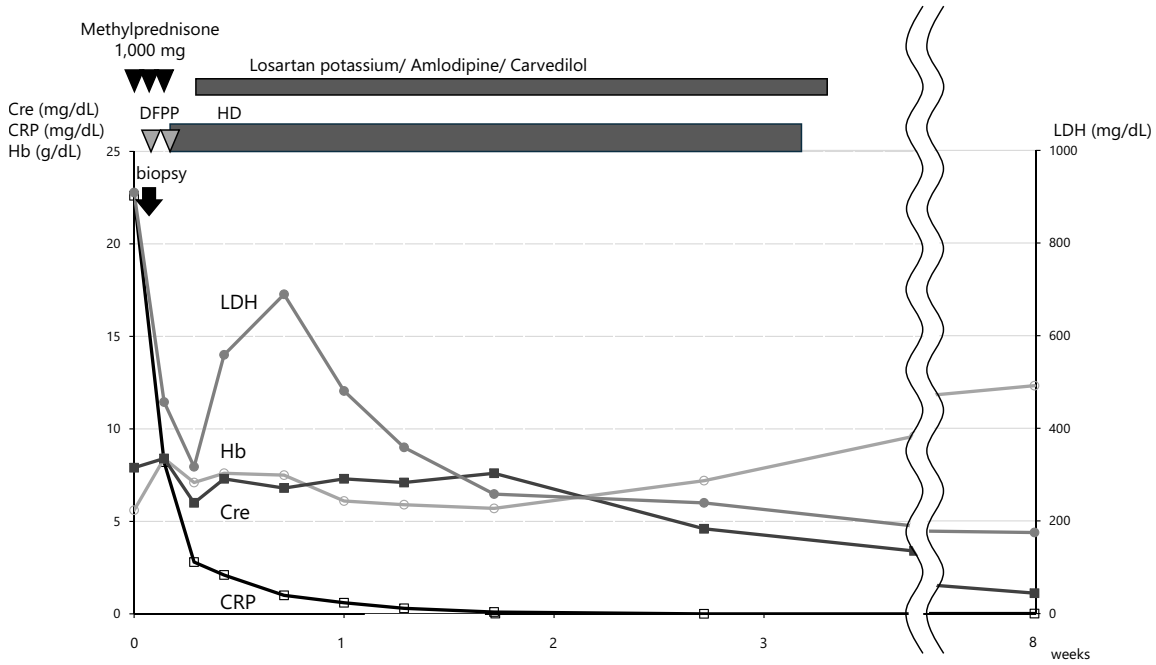

Fig. 3 Clinical course. DFPP: double-filtration plasmapheresis, HD: hemodialysis, Cre: serum creatinine, Hb: hemoglobin, LDH: lactate dehydrogenase

12], and Upshaw–Schulman syndrome [13]. Coexistence of HUS was also characteristic in patients with these underlying diseases, which were classified as a secondary category of hypertensive renovascular diseases [5]. In the above-mentioned secondary diseases, hypertension has an acute onset, and the rapid rise in blood pressure can be assumed to be related to the formation of characteristic pathological renal lesions. Clinical characteristic may represent the difference between patients with these secondary diseases and those with malignant hypertension, although the renal tissue is similar. Malignant hypertension has the common feature of left ventricular hypertrophy, as evidenced by a long history of untreated hypertension in our case and in the cases reported by Nonaka et al., while, in secondary diseases, the finding of left ventricular hypertrophy is rare, because there is no prolonged hypertension. In patients with malignant hypertension, long-standing untreated hypertension may result in malignant nephrosclerosis if the hypertension worsens as a result of an additional particular factor. In patients with secondary diseases, hypertension is induced newly in a background with no history of untreated hypertension. Textbooks have named this disease malignant hypertension because the disease was fatal, and reported the pathological finding of fibrinoid necrosis at autopsy as a typical indicator of severe disease [1, 3]; however, our case illustrates the clinical course of this disease and shows that despite the severe renal pathology, renal function can normalize after successful treatment.

The severe alveolar hemorrhage in this case is not seen in malignant hypertension or hypertensive emergency disease and has not been reported in the numerous case reports by Nonaka et al. [2]. It is unclear whether vasculitis can really be ruled out in this regard. Furthermore, plasma exchange and initial steroid pulse therapy seem to have improved the prognosis. On the other hand, even if vasculitis with alveolar hemorrhage is considered, there have been no reports of malignant hypertension-like complications with severe retinopathy and hypertension. Furthermore, the absence of recurrence of vasculitis after short-term discontinuation of steroid therapy seems to be different from that of vasculitis syndrome. Malignant hypertension usually occurs in males around 40 years of age, and rarely occurs in female patients in their 20s, as in the present case. Therefore, it is expected that malignant hypertension-like symptoms in women in their 20s will be proposed as a different disease entity in the future, rather than applying this case to the usual malignant hypertension. Vasculitis that develops from the interlobular artery to the glomerulus is explained by ANCA-associated vasculitis, but the possibility of polyarteritis nodosa (PN) should be considered when ANCA is negative. However, glomerular lesions due to PN are not common, and it is known that extra-renal organ lesions such as skin lesions and high CRP levels are seen at the same time, but these findings corresponding to PN were not observed in this case. Fibromuscular dysplasia-type renovascular hypertension is important for the differential diagnosis of refractory hypertension

in young female patients. However, it is usually diagnosed by abnormal renal morphology and significant stenosis of the main trunk of the renal artery on imaging, without evidence of rapidly progressive nephritis, which is usually seen in malignant hypertension. FSGS has been reported on kidney biopsy of the healthy kidney [14], and ischemic nephropathy lesions have been reported in the affected kidney [14, 15], but no malignant nephrosclerosis-like lesions have been reported. In this case, renal imaging after renal function improvement did not show significant renal artery stenosis. There are scattered reports of diffuse alveolar hemorrhage being a rare complication of severe hypertension. No significant disease entity has been reported as a causative disease in previous reports. This syndrome may be the equivalent [16]. Endocrine hypertension, including pheochromocytoma, can be a differential diagnosis. However, these are chronic lesions and do not have the clinical presentation of rapidly progressive nephritis, and neoplastic lesions of the adrenal glands and other endocrine glands usually become evident during the course of the disease. In this case, no obvious endocrine disease has appeared in more than 10 years.

In summary, kidney biopsy in our patient showed severe TMA lesions, and the patient temporarily required dialysis; however, renal function was recovered by treatment with antihypertensive drugs.

Declarations

Conflict of interest The authors declare no competing financial interests and no conflicts of interest.

Ethical approval The present study adhered to the Declaration of Helsinki, and the patient gave her consent for the case report to be published.

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