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Case Report

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A Case of Malignant Hypertension-Induced Thrombotic Microangiopathy with Gradually Improved Renal Function Using Appropriate Antihypertensives

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Abstract

Malignant hypertension sometimes causes microangiopathic hemolytic anemia (MAHA) and thrombotic microangiopathy (TMA). TMA results in the obstruction of arterioles and capillaries due to microvascular thrombosis. The pathological diagnosis of TMA is done by tissue biopsy. In this process, malignant hypertension-induced TMA must be distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolitic uremic syndrome (HUS). We describe the case of a 45-year-old man with malignant hypertension, MAHA, and severe renal failure. Plasmapheresis was performed until the ADAMTS -13 activity was reported as normal. The patient's blood pressure was reduced in a controlled manner first using antihypertensives, and TMA was confirmed by a kidney biopsy. Based on the normal ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity, other possible conditions that might cause TMA were eliminated, and malign hypertension-induced TMA was diagnosed. After two years, the glomerular filtration rate was found to have increased from 22 to 59.5 ml/min. In cases of severe hypertension associated with TMA, it may sometimes not be easy to establish whether TMA is caused by malignant hypertension or other associated diseases. The treatment of hypertension-induced TMA aims to control hypertension, which leads to the resolution of TMA over time.

Keywords: Malignant hypertension, thrombotic microangiopathy, microangiopathic hemolytic anemia

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INTRODUCTION

Malignant hypertension (MH) is the most clinically severe form of hypertension characterized by an extremely high blood pressure (diastolic above 130 mm Hg) associated with bilateral retinal hemorrhages and/or exudates and papilledema (1). The general definition of MH does not consider other hypertensive target organ damage (kidney, heart, or brain associated with thrombotic microangiopathy) other than the eye, whereas the overall prognosis is largely dependent on the level of the effect on other target organs (2). Furthermore, the absence of fundus abnormalities does not exclude MH (3). Therefore, it may make more sense to use hypertension-induced multiple organ damage as a term rather than MH in identifying true urgencies (2). MH has low prevalence in the general population, with an annual incidence rate of around 5/100,000 in the Caucasian population (4). The prevalence of the coexistence of TMA and MH varies in different publications, being reported as 44% (7/16) by Akimoto et al. (5) and 27% (26/97) by van den Born (6); however, these authors did not perform renal biopsies and their results were based on laboratory tests.

Herein, we report a rare case of MH with MAHA, which was associated with biopsy-proven TMA in the kidney.

CASE PRESENTATION

A 45-year-old male patient, with no previously known disease, was presented with abdominal pain radiating to the left side. On admission, his blood pressure was 221/167 mm Hg (without left-right difference), and the pulse rate was 100 beats per minute and regular. The

results of the laboratory tests were as follows: creatinine: 3.16 mg/dL (glomerular filtration rate-eGFR: 22.3 mL/min), LDH: 1464 u/L, total bilirubin: 2.5mg/dL, direct bilirubin: 0.64 mg/dL, hemoglobin: 9.3 gr/dL, platelet count: 54.000 K/mm^3, haptoglobin: 29.5 mg/dL (30-200), reticulocytes: 5.79% (0.5-1.5), aldosterone: 6.27 ng/dL, renin: 6.67 ng/mL/h, and potassium: 2.97 mEq/L. Red cell fragmentation and schistocytes was seen on peripheral smear. In the urine analysis, there were 610 erythrocytes and 123 leucocytes, and the urine sediment was bland. There was 0.740 mg/mg proteinuria in the spot urine. The case was classified as Grade III retinopathy according to the Keith, Wagener, and Barker classification. The patient denied using illicit drugs. A standard work up was performed for secondary hypertension, including renovascular hypertension, primary aldosteronism, Cushing syndrome, pheochromocytoma, hypothyroidism, and hyperthyroidism; secondary hypertension was excluded with normal results. In addition, therapeutic plasma exchange (PEX) was performed five times until the ADAMTS13 activity was reported to be normal. During the follow-up, chronic lacunar infarcts were found on the brain CT, which was performed due to numbness in the left half of the patient, and the brain MRI revealed subcortical white matter and hyperintense foci in both cerebral hemispheres. The patient's blood pressure was reduced in a controlled manner first using intravenous nitroglycerin. Then, short-acting calcium channel blocker, beta-blocker, and aldosterone antagonist were prescribed. The LDH level dropped, and the platelet count increased. Due to the young age of the patient and for ruling out other renal illnesses, a renal biopsy was performed, which showed significantly thickened walls of the afferent arterioles, narrowed lumen, an onion membrane appearance, arteriolar hyaline material accumulation, significantly thickened walls of the arteries, intimal fibrosis, elastic lamina duplication, and thrombus at the entrance to the glomerular arteriole in two areas, as well as an associated ischemic segmental necrosis (Figures 1 and 2).

The patient was discharged on day 17 with a normal platelet count and LDH level; blood pressure was 150/100 mm Hg using antihypertension medications including calcium channel blocker, beta blocker, and spironolactone. Spironolactone was discontinued because of gynaecomastia, and angiotensin-converting enzyme inhibitors were started in follow-up. After two years, his creatinine level was 1.39 mg/dL (eGFR: 59.5 mL/min).

Written informed consent was obtained from the patient.

Main Points

- Malignant hypertension sometimes causes microangiopathic hemolytic anemia (MAHA) and thrombotic microangiopathy (TMA).
- Malignant hypertension-induced TMA must be distinguished from thrombotic thrombocytopenic purpura and hemolitic uremic syndrome.
- We describe a case with malignant hypertension, MAHA and severe renal failure. TMA was confirmed by a kidney biopsy. Other causes of TMA were ruled out.
- Plasmapheresis was performed until the ADAMTS -13 activity was reported as normal.
- The patient's blood pressure was reduced in a controlled manner. After two years, the glomerular filtration rate was found to have increased from 22 to 59.5 mL/min.

DISCUSSION

The current case presented with a clear clinical picture of MH and MAHA, and the presence of TMA was diagnosed by a kidney biopsy. The pathophysiologic mechanisms underlying TMA in MH are not yet fully understood. One explanation is the marked activation of renin-angiotensin-aldosterone system (RAAS) (probably due to juxtaglomerular ischemia) and the macrovascular and microvascular endothelial dysfunction (7). When hypertension is very severe and/or long-lasting, nitric

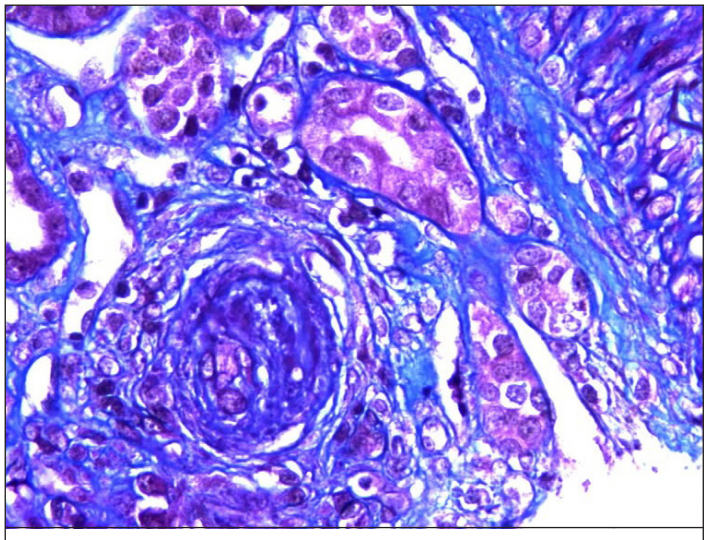

Figure 1. Appearance of the onion membrane, arteriolar hyaline material accumulation (Trichrome, ×40)

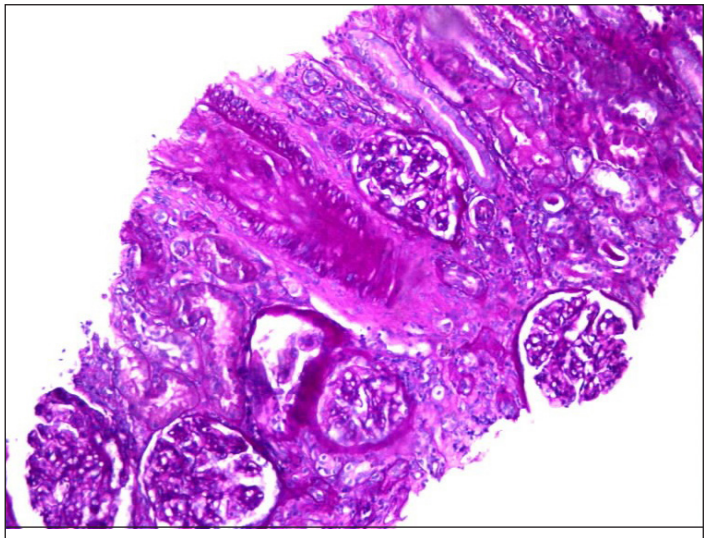

Figure 2. Intimal fibrosis, elastic lamina duplication (PAS, ×40)

oxide (NO) secretion (compensatory endothelial vasodilator response) is insufficient, and endothelial damage begins when a vasoconstricting substance, such as angiotensin II promotes the expression of proinflammatory cytokines. This endothelial dysfunction and NO depletion result in platelet aggregation and vasoconstriction (8).

Differential diagnosis of primary or secondary TMA varies greatly in terms of the treatment (9). Primary TMA syndromes include thrombotic thrombocytopenic purpura (TTP) (a severe deficiency of ADAMTS13 represented by an activity level of <10%), Shiga toxin-mediated hemolytic uremic syndrome (HUS), drug-induced TMA syndromes, complement-mediated TMA, and a rare hereditary disorder of vitamin B12 metabolism (9). Examples of secondary TMA are pregnancy-associated syndromes, severe hypertension, systemic infections and malignancies, autoimmune disorders, such as systemic lupus erythematosus, systemic sclerosis, complications of hematopoietic stem cell or solid organ transplantation, and disseminated intravascular thrombosis (9). In TTP/HUS, extremely severe thrombocytopenia (<20,000/µl), presence of hypertension without retinal findings, history of TMA and/or thrombocytopenia without hypertension, and no recovery of thrombocytopenia or hemolysis through blood pressure control without performing plasmapheresis can be observed (10).

A possibility of MH-induced TMA was considered in our patient due to the marked hypertension with left ventricular hypertrophy, grade III retinopathy, high creatinine level, and relatively high thrombocytopenia.

CONCLUSION

In cases of severe hypertension associated with TMA, it may sometimes not be easy to establish whether TMA is caused by MH or another disease in the absence of drug use or known conditions. TTP/HUS form that usually responds well to PEX can be predicted using certain clinical findings and laboratory results before the ADAMTS13 activity result is obtained; however, the ADAMTS13 activity level still provides more reliable data for the diagnosis of TTP.

Informed Consent: Written informed consent was obtained from the patient.

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