Malignant Hypertension with Thrombotic Microangiopathy

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Abstract

A 49-year-old man with malignant hypertension, acute kidney injury and mental deterioration was referred to our hospital. We initially observed microangiopathic hemolytic anemia, thrombocytopenia and kidney damage, indicating he had thrombotic microangiopathy (TMA). We considered TMA was caused by malignant hypertension and therefore did not start plasma therapy. The French TMA reference center reported that platelet counts and serum creatine levels have high values for predicting severe ADAMTS13 deficiency. The patient fully recovered from his illness after treatment with antihypertensive drugs and intermittent hemodialysis. This case might thus be useful to understand the proper differential diagnosis and treatment of TMA.

Key words: thrombotic microangiopathy, malignant hypertension, hypertensive emergency

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Introduction

Thrombotic microangiopathy (TMA) describes a pathological process of microvascular thrombosis, consumptive thrombocytopenia, and microangiopathic hemolytic anemia (MAHA), leading to ischemic organ damage (1). TMA syndrome is divided into primary TMA and secondary TMA (1). The syndromes of primary TMA have defined abnormalities that require specific treatment, such as ADAMTS13-mediated TMA [also known as thrombotic thrombocytopenic purpura (TTP)], Shiga toxin-mediated TMA [also known as hemolytic uremic syndrome (HUS)], drug-mediated TMA, complement-mediated TMA (atypical HUS), and cobalamin-mediated TMA (1). Secondary TMA syndrome is caused by some underlying disease, such as infection and collagen disease. These diseases include malignant hypertension, preeclampsia, hemolysis, elevated liver enzyme, and low platelets (HELLP) syndrome, systemic infections, malignancies, autoimmune disorders (such as systemic lupus erythematosus, antiphospholipid antibody syndrome, and scleroderma renal crisis), hematopoietic stem cell or organ transplantation, and disseminated intravascular coagulopathy (1).

If patients who present with an altered mental status and impaired renal function develop TMA, then empirical therapy with plasma exchange or plasma infusion should be initiated in most cases due to the difficulty in ruling out TTP at presentation. Although this approach has been widely accepted (2, 3), unnecessary and potentially harmful plasma exchange or plasma infusion should be avoided if possible. We herein present a case of TMA caused by malignant hypertension. We experienced a favorable clinical outcome in our patient without plasma exchange according to careful consideration of the differential diagnosis from TTP by predicting the ADAMTS13 activity from high platelet counts and elevated serum creatine levels based on the previous study by the French TMA reference center (4).

Case Report

A 49-year-old man with a history of untreated hypertension was admitted to another hospital with shortness of breath, an extremely high blood pressure of 240/140 mmHg, and evidence of acute kidney injury (blood urea nitrogen, 141 mg/dL; serum creatinine, 8.95 mg/dL; positive granular cast). He was originally diagnosed as having hypertension when he was approximately 30 years of age. His blood pres-
The results from these laboratory tests. Intravascular coagulation (DIC) was excluded according to non-immunological hemolytic anemia. Disseminated level was low and a direct Coombs test was negative, indicating that he had hypertension for a certain time (Fig. 1). The blood urea nitrogen level was more than two schistocytes per high-power field without microangiopathic hemolytic anemia (data not shown). Magnetic resonance imaging of the brain showed high intensity signals in the bilateral cerebral white matter on fluid-attenuated inversion recovery, suggesting posterior reversible encephalopathy syndrome (PRES).

After he was admitted to the previous hospital, he was diagnosed with malignant hypertension and treated with intravenous furosemide, oral amlodipine, and candesartan. Despite this treatment, he had a worsening renal function and gradually developed an altered mental status. Four days later, he was referred to our hospital for urgent hemodialysis. He did not have a recent history of infectious gastroenteritis or diarrhea. On this physical examination, his blood pressure was 170/84 mmHg, pulse was 86 beats per minute, and body temperature was 36.0°C. His Glasgow Coma Scale was 13 (E3V4M6) without notable focal neurological signs. A funduscopic examination showed hypertensive retinopathy, indicating he had hypertension for a certain time (Fig. 1). The rest of the examinations were unremarkable.

A complete blood count showed that the white blood cell count was 7,700/μL, with 84% neutrophils and 5% lymphocytes, hemoglobin level was 10.4 mg/dL, and the platelet count was 97×10^9/L. A peripheral blood smear revealed more than two schistocytes per high-power field without leukemic blast cells. The blood urea nitrogen level was 148.1 mg/dL and the creatinine level was 11.0 mg/dL. The lactate dehydrogenase (LDH) level was 473 IU/L. Liver function tests were normal. The prothrombin time, activated partial thromboplastin time, and serum fibrinogen and FDP levels were within normal limits. The D-dimer level was only slightly increased to 1.1 μg/mL. The serum haptoglobin level was low and a direct Coombs test was negative, indicating non-immunological hemolytic anemia. Disseminated intravascular coagulation (DIC) was excluded according to the results from these laboratory tests.

Computed tomography of the head revealed bilateral broad low-density areas in the cerebral white matter, suggesting leukoencephalopathy (data not shown). Magnetic resonance imaging of the brain showed high intensity signals in the bilateral cerebral white matter on T2-weighted images and fluid-attenuated inversion recovery with an increase in the apparent diffusion coefficient, compatible with posterior reversible encephalopathy syndrome (PRES) (Fig. 2). Abdominal computed tomography showed normal-sized kidneys without hydronephrosis.

According to these findings, the patient was diagnosed with malignant hypertension. Emergent dialysis was performed and intravenous antihypertensive therapy with nicardipine was initiated to achieve a normal blood pressure within several days. We presumed that ADAMTS13-deficient TTP was unlikely, as his platelet counts (97×10^9/L) and serum creatinine levels (11.0 mg/dL) at presentation were elevated according to the cut-off values provided in the previous report by the French TMA reference center (4). With several courses of intermittent hemodialysis and control of his blood pressure, the patient’s altered mental status completely resolved, and thrombocytopenia and the renal function dramatically improved (Fig. 3). It took 7 days until we obtained the results of the ADAMTS13 activity and inhibitor, because it was not covered by the Japanese public health insurance. The ADAMTS13 activity was 61% and ADAMTS13 inhibitors were negative, indicating that TTP was excluded. A stool culture was negative for Shiga toxin-producing Escherichia coli. The serum cobalamin levels were within the normal limits. Antinuclear antibody, antiphospholipid antibody, and antineutrophil cytoplasmic antibody were negative. These findings excluded HUS, cobalamin deficiencies, and collagen diseases. Although his serum creatinine level remained as high as 4.5 mg/dL, we successfully stopped intermittent hemodialysis. On hospital day 40, he was discharged from the hospital with normal platelet counts. A standard work-up for secondary hypertension, such as renovascular hypertension, primary aldosteronism, Cushing syndrome, pheochromocytoma, hypothyroidism,
and hyperthyroidism, was performed. However, the screening tests were all negative other than subclinical hyperthyroidism, which returned to a euthyroid status during the follow-up. Therefore, we concluded that the patient’s malignant hypertension was derived from untreated essential hypertension.

Discussion

If TTP cannot be ruled out in patients presenting with TMA, then empirical therapy with plasma exchange or plasma infusion should be initiated because of the high mortality of TTP without treatment (1). In cases where TTP or atypical HUS cannot be excluded at initial presentation, plasma exchange should be continued until the results of the ADAMTS13 activity and its inhibitors are obtained. This is because the ADAMTS13 activity is highly useful for distinguishing these two conditions (2, 3). TTP is more likely if TMA improves by plasma exchange.

Although this clinical approach has been widely accepted, unnecessary plasma exchanges have been performed for patients whose final diagnosis was not TTP (5). Because plasma exchange is an expensive procedure and confers the risk of developing a catheter-related bloodstream infection and/or allergic reactions to the plasma, unnecessary and potentially harmful plasma therapy should be avoided as much as possible (6).

A recent study showed that the platelet count and serum creatinine levels are strong predictors of acquired ADAMTS13 deficiency. In a cross-sectional study performed by the French TMA center that studied 214 patients with TMA (4), the platelet count was significantly lower in patients in the ADAMTS13 deficiency group [mean (standard deviation), 17.4 (14.2) × 10^9/μL] compared with those in the ADAMTS13 detectable group [66.6 (49.3) × 10^9/μL]. Additionally, the serum creatinine levels were significantly lower in the deficiency group [1.29 (0.77) mg/dL] than in the detectable group [5.13 (3.68) mg/dL] (4).

Recently, Kato et al. developed a new immunoassay to rapidly measure the ADAMTS13 activity using gold particles and an automated machine (7). Although a laboratory test of the ADAMTS13 activity is essential for the differential diagnosis of TTP from other TMA, it is not covered by the Japanese public health insurance. Therefore, it is valuable to predict severe ADAMTS13 deficiency by the platelet counts and serum creatine levels (4).

In our case, TMA was diagnosed at presentation because of Coombs-negative hemolytic anemia with schistocytes and thrombocytopenia. We presumed that TTP was unlikely because the platelet count and serum creatinine level were much higher than the cut-off point in the previous study (4). Additionally, the cause of TMA was malignant hypertension according to the presence of hypertensive retinopathy and PRES, which enabled us to avoid unnecessary plasma exchange. A past history of hypertension, high mean arterial pressure, and significant renal impairment, but relatively modest thrombocytopenia, can also be clues for diagnosing malignant hypertension-induced TMA, according to a recent study (8).

Malignant hypertension often causes TMA (9, 10). Activation of the renin-angiotensin-aldosterone system and the subsequent endothelial damage play a central role in the pathogenesis of TMA in malignant hypertension (11). Angiotensin II has direct cytotoxic effects on vessel walls. As compensation for activation of the renin-angiotensin-aldosterone system and increased vascular resistance, endo-
thelial cells secrete vasodilator substances, such as nitric oxide (NO). When hypertension is so severe and/or sustained, this compensatory endothelial vasodilator response is overwhelmed, and endothelial damage is induced by a pro-inflammatory cytokine response. This endothelial dysfunction leads to the depletion of NO, which contributes to platelet aggregation and vasoconstriction. TMA then occurs in malignant hypertension via increased superoxide anions in a NO-dependent manner (12). Furthermore, increased levels of superoxide anion can reduce the bioactivity of NO. In addition, free hemoglobin, which is released from erythrocytes to the plasma in severe hemolysis, can scavenge NO (13).

Primary TMA syndromes often lead to an impaired kidney function with subsequent severe hypertension. A total of 13% of patients with TMA were reported to develop malignant hypertension (14). While differentiating these two phenomena is challenging, an improvement of MAHA and thrombocytopenia after emergent dialysis and antihypertensive therapy without plasma exchange or immunosuppressive therapy also suggests secondary TMA due to malignant hypertension (15). In addition, plasma exchange is theoretically ineffective for the management of secondary TMA due to malignant hypertension (16) and other systemic diseases. Although there is a case report in which TMA due to malignant hypertension was successfully treated with plasma exchange and intravenous antihypertensive therapy (17), it remains unclear which patients need plasma exchange. Further studies are necessary to clarify the indications for plasma therapy for secondary TMA.

In conclusion, we herein presented a case of TMA caused by malignant hypertension. We believe this case report might be useful to understand the differential diagnosis and proper management of TMA in the daily clinical practice.

The authors state that they have no Conflict of Interest (COI).

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