Case Report

Thrombotic Microangiopathy in Malignant Hypertension and Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP): Can We Differentiate One from the Other?

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Patients with malignant hypertension sometimes exhibit microangiopathic hemolytic anemia/thrombocytopenia known as thrombotic microangiopathy (TMA). On the other hand, severe hypertension is sometimes associated with hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP). Because the clinical features of the two entities overlap significantly, it is sometimes difficult to distinguish one from the other. However, such differentiation is indispensable, since early performance of plasmapheresis is critical in HUS/TTP. It has been suggested that severe thrombocytopenia is one of the most useful differential points in diagnosing HUS/TTP from malignant hypertension caused by other etiologies. Early performance of plasmapheresis can be justified in the presence of both TMA and thrombocytopenia. However, thrombocytopenia can be seen in the cases with malignant hypertension from etiologies other than HUS/TTP, and in these particular cases, plasmapheresis is useless and can be harmful. Recently, the plasma level of ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), which is a von Willebrand Factor cleaving protease, has been shown to be very low in familial or some of the sporadic cases of TTP, and a low level of ADAMTS13 is very specific to TTP. Some reports have shown that patients with a very low plasma level of ADAMTS13 respond very well to plasmapheresis. We recently experienced two cases with TMA. Although both of our patients had severe hypertension with TMA, different therapeutic strategies ameliorated their illness: symptomatic treatment was effective in case 1, which showed normal ADAMTS13 activity, whereas plasma infusion was necessary to save case 2, which showed low ADAMTS13 activity. Thus, patients with a low level of ADAMTS13 activity might respond well to plasmapheresis or plasma infusion. When presented with patients with severe hypertension and thrombotic microangiopathy, ADAMTS13 activity may prove to be a promising adjunctive tool in differentiating TTP from TMA due to other etiologies, but in the meantime, we should make the choice of whether or not to perform plasmapheresis based on the degree of thrombocytopenia. (*Hypertens Res* 2005; 28: 89–95)

Key Words: malignant hypertension, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, thrombotic microangiopathy, ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), plasmapheresis

Introduction

Malignant hypertension is a clinical syndrome characterized

by severe hypertension and organ damage, including progressive renal failure, heart failure and encephalopathy, and often associated with microangiopathic hemolytic anemia. The pathology of organ damage in malignant hypertension is typ-

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ically characterized by fibrinoid necrosis, fibrin and platelet clots in the lumina of arterioles and resultant luminal narrowing leading to excess fragmentation of erythrocytes and consumption of platelets. This pathological finding is called thrombotic microangiopathy (TMA) (1, 2).

TMA is defined as a lesion that causes partial or complete obstruction of the vessel lumina *via* the microvascular aggregation of platelets, in addition to vessel wall thickening with endothelial cell injuries (3, 4). Laboratory characteristics of TMA include hemolytic anemia, thrombocytopenia and elevated serum level of lactate dehydrogenase (LDH) (5). TMA is regarded as indicating either hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) (3). However, HUS and TTP are syndromes rather than diseases, and their pathogeneses are diverse. Moreover, clinical or laboratory features of TMA are shared by many diseases other than HUS/TTP (5), and the broad definition of TMA encompasses these diseases (Table 1). Among them, malignant hypertension is well known to present with features of TMA (1, 2), and the diagnosis of one from the other etiology of TMA is often difficult. The recently elucidated pathogeneses of some forms of HUS/TTP may have an impact on the strategy of its management. In particular, discovery of the von Willebrand factor (VWF) cleaving protease, which is also known as ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), and the finding that a deficiency of this enzyme or the presence of its inhibitor is involved in the pathogenesis of TTP provided new insight into management of TTP and a new diagnostic tool for differentiating TTP from other etiologies of TMA (6, 7).

Here we describe two illustrative cases of TMA presenting with severe hypertension. Based on these cases, we discuss the pathogenesis of TMA and propose a possible method to differentiate TTP from other etiologies of TMA, including malignant hypertension.

Case Report

Case 1

A 33-year-old man was presented to the emergency room for nausea and epistaxis. He had eaten Thai food a week earlier and general malaise and nausea developed afterwards. He had a history of hypertension in his adolescence but he had never sought medical attention and had never been medically treated. He denied any use of illicit drugs. On admission, his blood pressure was 160/120 mmHg, which rose significantly after hydration and required intravenous anti-hypertensive medication. Fundus examination revealed significant cotton exudates in both retinas. He had microangiopathic hemolytic anemia (hemoglobin 9.0 g/dl) with anisocytosis, lactate dehydrogenase (LDH: 1,059 IU/l, normal reference level 115–245 IU/l) and thrombocytopenia (69,000/ l). After admission, his serum creatinine level rose from 4.59 to 7.59 mg/dl, which required 2 sessions of hemodialysis. Also, he developed

abdominal pain of undetermined etiology with a fluctuation of serum LDH level. Although he was treated only symptomatically, his hemoglobin and platelet count gradually rose and his serum LDH fell towards normal. His renal function also gradually recovered afterwards. He was discharged on day 28 after admission with a normal platelet count and without anisocytosis. His plasma ADAMTS13 activity on day 80 was normal (68%; more than 20% is considered normal clinically) and the ADAMTS13 inhibitor was at an undetectable level in his plasma. His serum creatinine at 6 months from discharge was down to 2 mg/dl.

Case 2

A 2-year-old boy was presented to the emergency room for hemiparesis after head injury. He had an episode of infantile jaundice treated with phototherapy and exchange blood transfusion. Subsequently he had an episode of purpura and thrombocytopenia without apparent cause, which had been diagnosed as idiopathic thrombocytopenic purpura. On admission, he was found to have intracranial bleeding, high renin hypertension with blood pressure of 160/120 mmHg, acute renal failure and TMA. He was diagnosed as having idiopathic HUS/TTP and successfully treated with plasma infusion. Thereafter, he required a plasma infusion every other week to maintain his platelet count, and had several episodes of acute renal failure and worsening of TMA with or without severe hypertension. He is now 31 years old and doing well with plasma infusion. His recent plasma ADAMTS13 activity was less than 3%. Because of his disease history since infancy, he was suspected of having familial TTP (Upshaw-Schulman syndrome [USS]), and his and his parents' blood were sent for gene analysis for *ADAMTS13*. He was found to be a compound heterozygote of the *ADAMTS13* gene mutation (the combination of a missense mutation in exon 7 [H234Q] inherited from his father and a non-sense mutation in exon 26 [R1206X] inherited from his mother). Based on these findings, he is now diagnosed with USS.

As described in the above two cases, plasma ADAMTS13 activity might be associated with etiologies of TMA; typical TTP is associated with low ADAMTS13 activity, and other etiologies of TMA are associated with normal ADAMTS13 activity. Recently, a very interesting case was reported by Vuylsteke *et al.* (8). The patient was a young woman who had an episode of severe hypertension and mild thrombocytopenia (platelet count 50,000/ l) which remitted only with blood pressure control. This patient had recurrent episodes of mild thrombocytopenia and microangiopathic hemolytic anemia with low ADAMTS13 activity, which led to a diagnosis of TTP. This case was similar to our case 1 but had low ADAMTS13 activity, and therefore was correctly diagnosed as a case of TTP with coincident malignant hypertension. This case illustrates how difficult it is to differentiate "mild" TTP from TMA secondary to malignant hypertension.

Discussion

Pathogenesis of TMA in Malignant Hypertension

It is well recognized that severe hypertension often accompanies TMA (2, 9). Although the frequency of systemic TMA in cases with malignant hypertension has not been well described in the literature, it seems relatively common, and intrarenal TMA is a typical histological finding in malignant hypertension with renal impairment (1). On the other hand, 13% of patients with systemic TMA have been reported to show malignant hypertension (10). TMA is thought to be caused by excess fragmentation of erythrocytes passing through the narrowed vascular lumen and an excess consumption of platelets activated by the injured endothelium, although the exact pathogenesis has not been fully elucidated.

Malignant hypertension is characterized by severe hypertension, multi-organ dysfunction associated with TMA and activation of the renin-angiotensin-aldosterone system (RAAS). The role of RAAS in the pathogenesis of malignant hypertension was first recognized by a series of studies in stroke prone spontaneously hypertensive rats (SHR-SP). In SHR-SP, RAAS was paradoxically activated with salt loading and accompanied TMA with fibrinoid necrosis of organ arterioles (11). The blockade of the RAAS system by angiotensin converting inhibitors (12), angiotensin II receptor antagonist (13), or aldosterone receptor antagonist (14) has been shown to ameliorate TMA in this setting. Recently, some investigators have suggested that aldosterone may have a pivotal role in the pathogenesis of TMA (15).

As shown in Fig. 1, it is postulated that the endothelial dysfunction caused by RAAS activation has a central role in the pathogenesis of malignant hypertension (1). In the setting of severe hypertension associated with activation of vasoconstricting RAAS, the endothelial cells secrete vasodilating substances such as nitric oxide and adrenomedullin or prostacyclin to compensate for the change in vascular resistance. If hypertension is severe enough and/or prolonged, this compensatory mechanism fails and a vasoconstricting substance such as angiotensin II promotes expression of proinflammatory cytokines. These series of events subsequently damage the endothelium further and activate a coagulation cascade leading to fibrinoid necrosis, edema of arterioles and local platelet aggregation. TMA has been attributed to the mechanical stress that red blood cells are subjected to when passing through the narrowed lumen of arterioles with fibrinoid necrosis and perivascular edema (16).

The treatment of TMA in the setting of malignant hypertension consists of rapid control of hypertension with or without RAAS antagonists. Theoretically, there should be no place for plasmapheresis in the management of TMA in malignant hypertension.

Pathogenesis of TMA in Malignant HTN, HUS and TTP

Fig. 1. Pathogenesis of TMA in malignant HTN, HUS and TTP. Malignant HTN, HUS and TTP are all causes of endothelial damage through various mechanisms, including shear stress, activated RAAS and Shiga toxin. Shear stress or endothelial damage leads to activation of various cytokines and vasoconstrictive agents to promote intravascular platelet aggregation, coagulation and narrowing of the vascular lumen, and causes thrombosis of the arterioles, fibrinoid necrosis, microangiopathic hemolytic anemia and thrombocytopenia. TMA, thrombotic microangiopathy; HTN, hypertension; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; RAAS, renin-angiotensin-aldosterone system; TXA2, thromboxane A 2; ADAMTS13, a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13.

Pathogenesis of TMA in TTP and HUS: The Role of ADAMTS13

TTP and HUS are both characterized by TMA. The term TTP typically refers to a form of TMA which affects adolescents and adults and causes central nervous system disorders, whereas HUS often refers to a form of TMA which affects young children with *Escherichia coli* (*E. coli*) O157:H7 infection and involves the kidneys. Although TTP and HUS have different etiologies and clinical manifestations, they are mostly indistinguishable in their laboratory features and pathologies, and are often referred to as HUS/TTP. To make matters more complicated, because TMA develops in various disorders (Table 1), patients with these disorders are often labeled as having HUS, TTP or HUS/TTP irrespective of their underlying pathogenesis.

Patients with HUS/TTP typically have unusually large multimers of VWF. VWF is secreted from endothelial cells as a large polymer of the mature 220 kDa polypeptide. In the circulation, it undergoes cleavage by a protease named ADAMTS13 to a series of smaller multimers. The large VWF multimer tends to aggregate platelets when it is unfolded, especially under high shear stress, which is not the case for the smaller cleaved multimers (17). So a low level of plasma

ADAMTS13 activity caused by either genetic defects or its inhibitors causes intravascular platelet aggregation, especially when it is exposed to high shear stress, which leads to intravascular thrombosis and thrombocytopenia (Fig. 1).

Recently, a defect in the *ADAMTS13* gene was found to cause familial TTP (6), and an inhibitor of the protease has been shown to cause acquired recurrent TTP (6, 7). In these studies, patients with familial TTP had very low levels of plasma ADAMTS13 activity, and those with the acquired form had the ADAMTS13 inhibitors, whereas those with HUS had a normal level of ADAMTS13 activity.

A congenital form of familial TTP known as USS is caused by a defect of the *ADAMTS13* gene (18, 19). Patients with USS have either homozygotes or compound heterozygotes of the gene mutation (19–21). The clinical features of USS include severe hyperbilirubinemia with negative Coombs test soon after birth and recurrent episodes of TMA with ADAMTS13 activity below 3% and without the ADAMTS13 inhibitor. Plasma infusion dramatically ameliorates the abnormal clinical features but must be repeated every 2–3 weeks. This disease was formerly diagnosed as chronic relapsing TTP, congenital microangiopathic hemolytic anemia or familial HUS/TTP.

Although the potential usefulness of the plasma level of ADAMTS13 activity to differentiate TTP from HUS is still a matter of debate (22), such measurement may prove to be a new tool for the differential diagnosis (23). As stated above, the *E. coli* O157:H7 infection typically associated with pediatric HUS is associated with a plasma ADAMTS13 level of more than 0.8 U/ml (which is a normal ADAMTS13 level), whereas typical TTP (absence of any of the plausible causes shown in Table 1, no diarrhea, no renal failure/severe hypertension/pulmonary infiltrates, age more than 10 years) is associated with a plasma ADAMTS13 level of less than or equal to 0.1 U/ml (low-level ADAMTS13) (23). Some acquired forms of TTP, especially ticlopidine-associated TTP, have an undetectable level of plasma ADAMTS13, which has been attributed to the presence of IgG inhibitors of the protease (24).

In contrast, HUS has a different pathogenesis (Fig. 1). TMA in *E. coli* O157:H7 infection-induced HUS seems to be associated with local and systemic inflammation caused by Shiga toxin (3, 25). Shiga toxin enhances the secretion of proinflammatory cytokines and the expression of adhesion molecules on the cell surface, leading to coagulation cascade and platelet aggregation. It also promotes secretion of an unusually large VWF from the endothelial cells, to which platelets aggregate. Shiga toxin may promote endothelial cell death, which in turn causes denudation of the endothelium and releases tissue factors which further promote fibrin-associated platelet aggregation. These findings suggest that ADAMTS13 plays a small or no role in the pathogenesis of TMA, and there is no deficiency of ADAMTS13 in typical diarrhea-associated HUS (26). In support of the notion that the pathogenesis of platelet aggregation differs between TTP

Table 1. Differential Diagnosis of Microangiopathic Hemolytic Anemia with Thrombocytopenia (Thrombotic Microangiopathy)

Hemolytic uremic syndrome (<i>E. coli</i> -associated, familial, idiopathic)
Thrombotic thrombocytopenic purpura (familial, recurrent, idiopathic)
Malignant hypertension
Medication (cyclosporine A, tacrolimus, mitomycin, ticlopidine, clopidogrel, etc.)
Post organ/hematopoietic cell transplantation
Disseminated intravascular coagulation
Sepsis
Malignancy
Preeclampsia/eclampsia, HELLP syndrome
Systemic vasculitis (SLE, scleroderma, cryoglobulinemia, etc.)

E. coli, *Escherichia coli*; HELLP, hemolysis, elevated liver enzymes and low platelets; SLE, systemic lupus erythematosus.

and HUS, the components of thrombi in typical TTP have been shown to be made up of unusually large VWF and platelets, whereas those in *E. coli*-associated HUS are made up of fibrin and platelets, but not VWF (26).

These findings that a low plasma level of ADAMTS13 with or without ADAMTS13 inhibitors causes TMA may have some implications for the management of TMA in this particular setting. Because plasma contains ADAMTS13, a plasma infusion may be the treatment of choice until the recombinant or purified human ADAMTS13 becomes clinically available. If ADAMTS13 deficiency is caused by its inhibitors, plasmapheresis (plasma exchange) should be the treatment of choice rather than plasma infusion alone to remove the inhibitors. On the other hand, there is no theoretical rationale for treating *E. coli*-associated HUS with plasma infusion or exchange, because this condition is not associated with ADAMTS13 deficiency or the presence of its inhibitors circulating in the plasma (although some cases with familial HUS are associated with a deficiency of "Factor H" (27–29)). In fact, plasmapheresis in the setting of pediatric *E. coli*-associated HUS has been unsuccessful and is regarded as not indicated (30). Matsumoto *et al.* reported a very interesting observation of a relationship between the ADAMTS13 activity level and the response to plasmapheresis (31). They evaluated the efficacy of plasma exchange in 18 patients diagnosed with idiopathic TTP. Twelve of them had plasma ADAMTS13 activity of less than 3% and the rest showed activity of above 3%. Ten out of 12 patients with low ADAMTS13 activity had complete remission (CR), whereas only 2 out of 6 patients with normal ADAMTS13 activity had CR. All of 4 patients with ADAMTS13 activity of more than 20% died in spite of plasma exchange. Although this was a small clinical study, and more patients will be needed before drawing any definitive conclusions, it does suggest that patients with very low

Table 2. Possible Differential Points in Diagnosing Malignant Hypertension and Thrombotic Thrombocytopenic Purpura (TTP)/Hemolytic Uremic Syndrome (HUS) in Patients with Severe Hypertension and Thrombotic Microangiopathy

Points which favor diagnosis of malignant hypertension
<ul style="list-style-type: none"> • Extremely severe hypertension (diastolic blood pressure > 130 mmHg) • Past medical history of uncontrolled hypertension
Points which favor diagnosis of TTP/HUS
<ul style="list-style-type: none"> • Extremely severe thrombocytopenia (platelet count less than 20,000/ l) • Presence of hypertension but without retinal findings • History of TMA and/or thrombocytopenia without hypertension • No recovery of thrombocytopenia or hemolysis despite blood pressure control and without plasmapheresis

TMA, thrombotic microangiopathy.

ADAMTS13 activity tend to respond to plasmapheresis. These observations were recently confirmed by Zheng *et al.*, who reported that plasmapheresis led to complete remission and good prognosis in all of their HUS/TTP patients with low ADAMTS13 activity and without ADAMTS13 inhibitors, but patients with normal ADAMTS13 activity had a poor prognosis irrespective of whether or not they received plasmapheresis (32). As described above, ADAMTS13 activity might eventually become a good index to help in deciding whether plasmapheresis is indicated. At present, however, the assays for ADAMTS13 activity are time consuming, unstandardized, and not commercially available (23). Also, some cases with disease other than HUS/TTP, such as cases of disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, or systemic lupus erythematosus, have been reported to have low ADAMTS13 activity (33), and others suffering from adult HUS or TTP with detectable ADAMTS13 activity seemed to respond to plasmapheresis, although we do not know whether this was due to problems with the standardization of the ADAMTS13 assay or TTP remitted spontaneously irrespective of plasmapheresis (34). Thus, at this point, some researchers have recommended (22, 30) that we should not differentiate among various types of TTP and HUS, and should try plasmapheresis even if ADAMTS13 activity is normal when managing patients with suspicion of HUS/TTP (severe thrombocytopenia) but without a definitive diagnosis of the causes of TMA listed in Table 1.

Clinical Dilemma in Managing Patients with TMA and Severe Hypertension

What should we do when we encounter a case with TMA and severe hypertension? This is the situation when we need to distinguish malignant hypertension from TTP/HUS. Plasmapheresis should be initiated as soon as possible if we are dealing with TTP, because the prognosis is quite dismal (the mortality is more than 90%) without plasmapheresis (30, 35). On the other hand, plasmapheresis is an invasive therapy with possible significant complications, such as catheter-related infection and thrombosis and allergic reaction to plasma (30).

Moreover, plasma is very expensive and may transfer infection. So we should avoid plasmapheresis as much as possible when we are dealing with TMA other than TTP with low ADAMTS13 activity.

Patients with TTP/HUS typically have severe thrombocytopenia (platelet count less than 20,000/ l) (5) but do not have severe hypertension, although there are some exceptions (8, 36); the patient in the case described by Vuylsteke *et al.* was diagnosed with TTP with low ADAMTS13 activity and had mild thrombocytopenia and severe hypertension (8). On the other hand, severe thrombocytopenia with a platelet count less than 20,000/ l is not often seen in malignant hypertension (37). Table 2 shows possible differential points, but even these points may overlap. Therefore, for patients with TMA with severe hypertension, we suggest the approach summarized in Fig. 2. For the time being, we should consider plasmapheresis when patients have moderate to severe thrombocytopenia (a platelet count less than 20,000–50,000/ l; most of the reported cases of thrombocytopenia due to severe hypertension have platelet counts of more than 50,000/ l) (2, 38). Plasmapheresis should be performed daily until the platelet count returns to lower limit of normal range, and thereafter the frequency should be tapered (30). In patients with mildly to moderately decreased platelet counts and a mild degree of TMA, plasmapheresis might not be performed and blood pressure should be strictly controlled unless there is no recovery of thrombocytopenia and hemolytic anemia, because idiopathic HUS/TTP rarely remits spontaneously. An ADAMTS13 assay should be considered whenever possible to confirm the diagnosis of TTP, because we could have a sound reason to offer and continue plasmapheresis in these patients even when the response to plasmapheresis is delayed or suboptimal. On the other hand, if the ADAMTS13 activity is not low and the response to plasmapheresis is not good, early discontinuation of the therapy might be considered. However, the results of the assay should not affect the decision to perform plasmapheresis in the setting of severe cases of TMA (platelet count of less than 20,000/ l); plasmapheresis should be tried in all such cases (30).

Case 1 exhibited only mild to moderate thrombocytopenia

Fig. 2. A proposal for management of patients with TMA and severe HTN. When encountering a patient with TMA and severe HTN, check the platelet count first. If the platelet count is less than 50,000/ l, proceed to plasmapheresis even if a definitive diagnosis has not been made. If the platelet count is equal to or greater than 50,000/ l, check the clinical situation. If the degree of HTN is severe (e.g., systolic BP of more than 200 mmHg, or diastolic BP of more than 120 mmHg) or if the patient has a history of long-standing significant HTN, and if the thrombocytopenia or lactate dehydrogenase levels have a tendency to normalize only with BP control, plasmapheresis can be withheld. At the same time, ADAMTS13 activity may be checked, and, if the level is low, proceeding to plasmapheresis is reasonable. TMA, thrombotic microangiopathy; HTN, hypertension; BP, blood pressure; ADAMTS13, a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13.

and hemolytic anemia associated with longstanding hypertension. Thus, we suspected malignant hypertension more than HUS/TTP, and plasmapheresis was not given. This patient had almost normal ADAMTS13 activity (although the assay should have been done during the acute phase of TMA), which, along with the fact that the patient had a good outcome, confirmed for us that plasmapheresis was not needed in this particular case. Case 2 was a patient with familial HUS/TTP (Upshaw-Schulman syndrome) who had presented with severe high renin hypertension. Although severe hypertension accompanied only one episode out of many recurrences of TMA, this might have been confused with malignant hypertension causing the problem. The patient received a plasma infusion because of the severe degree of thrombocytopenia. We can speculate that his hypertension was partly due to the presence of acute renal failure. The case described by Vuylsteke *et al.* (8) illustrates how difficult it is to distinguish malignant hypertension from TTP/HUS, and the usefulness of an ADAMTS13 assay in determining the etiology and managing the patients. If the level of activity of the protease in plasma had not been checked in this patient, an accurate

diagnosis would not have been made.

Conclusion

In cases of severe hypertension accompanied with TMA, it is very difficult to determine whether the TMA is a form of TTP/HUS, which would respond well to plasmapheresis, or whether the TMA is a result of malignant hypertension or other disease. Although plasmapheresis should be given to all patients with severe TMA, the choice of treatment must be made based on clinical results when the degree of TMA is mild to moderate. Measurement of ADAMTS13 activity may be useful in diagnosing TTP and also in guiding the choice of therapy for patients with TMA and severe hypertension, although currently there is no standardized, widely available assay for this activity.

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