

Thrombotic Microangiopathy Presenting As Fulminating Rhabdomyolysis with Multiorgan Dysfunction

Nadeem Ikhtlaque, MD

Jae C. Chang, MD

The classic pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia (MAHA), renal dysfunction, and neurologic impairment defines thrombotic thrombocytopenic purpura (TTP). Traditionally, hemolytic uremic syndrome (HUS) has been considered a similar pathologic entity to TTP, the primary distinction being that the former condition predominantly involves the kidney. The term *thrombotic microangiopathy* (TM) has been introduced to encompass TTP, HUS, and (in some cases) HELLP syndrome (ie, hemolysis, elevated liver enzyme, and low platelet count in association with pregnancy), because these conditions have same hematologic features and involve similar pathologic changes.^{1,2} The essential diagnostic criteria for TM are unexplained thrombocytopenia and MAHA; the characteristic pathologic feature is diffuse arteriolar capillary microthrombi in the involved organs. The clinical manifestations of TM depend on specific organ dysfunction(s) involved. It is well recognized now that, in addition to the brain, kidney, and liver, TM can affect other organs, including the lung, heart, intestine, skin, eye, pancreas, and digits.³⁻¹⁰

We report a case of atypical TM presenting as fulminating rhabdomyolysis with multiorgan dysfunction (ie, dysfunction of the brain, lung, liver, pancreas, kidney). The clinical features of atypical TM that support its designation as a multisystem disorder are presented, and the possible pathophysiology and management of the disorder are discussed.

CASE PRESENTATION

Initial Evaluation and Management

A previously healthy 44-year-old man was admitted to the hospital with intermittent confusion and severe dehydration. He was not taking any medications and reported no alcohol ingestion prior to admission. Physical examination showed a somnolent, disoriented man with a temperature of 37.2°C (99°F), blood pres-

sure of 112/60 mm Hg, heart rate of 120 bpm, and respiratory rate 22 breaths/min. The abdomen was mildly tender in the epigastric region, and bowel sounds were diminished. On admission, hemoglobin level was 15.9 g/dL, hematocrit was 50%, leukocyte count was $16 \times 10^3/\text{mm}^3$, and platelet count was $344 \times 10^3/\text{mm}^3$. Blood urea nitrogen and serum creatinine levels were 74 mg/dL and 4.9 mg/dL, respectively; serum glucose level was 1410 mg/dL. The creatine kinase level was markedly elevated, at 3350 U/L. The serum lipase level was also elevated, at 7489 U/L, and the serum amylase level was elevated (746 U/L). The serum levels of the liver enzymes, including transaminases and alkaline phosphatase, were within normal limits, as were results of ultrasonography and a computerized tomographic scan of the abdomen. On the basis of the patient's clinical presentation and the laboratory data obtained, a diagnosis of a hyperosmolar state due to severe hyperglycemia associated with acute pancreatitis was made. The patient was treated with administration of intravenous fluids and regular insulin.

Continued Clinical Course

Twenty-four hours after admission to the intensive care unit, the patient developed fever (temperature to 38.8°C [102°F]) and became more confused and lethargic. Laboratory testing at this time showed decreases in a number of measurements: hemoglobin level was now 8.6 g/dL, hematocrit was 25.4%, and platelet count was $13 \times 10^3/\text{mm}^3$. Reticulocyte count was 2.4% of erythrocytes. A peripheral blood smear showed numerous schistocytes and prominent polychromasia (Figure 1). The serum lactate dehydrogenase level was 3052 U/L, and the serum haptoglobin level 99 mg/dL.

Dr. Ikhtlaque is Chief Resident, Internal Medicine, and Dr. Chang is a Professor of Medicine, Wright State University School of Medicine and Good Samaritan Hospital, Dayton, OH.

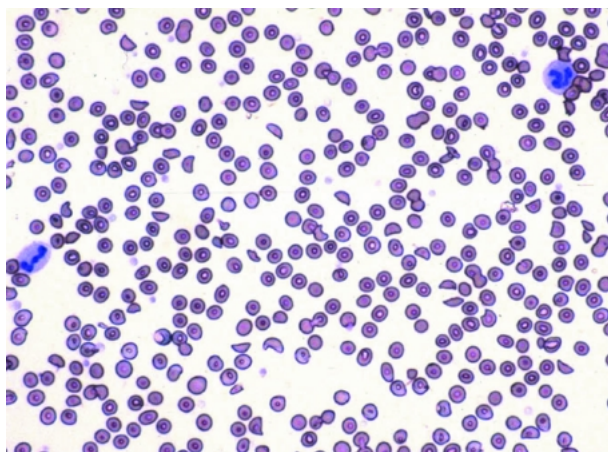


Figure 1. An initial blood smear from the case patient (prior to plasma exchange therapy) showing numerous schistocytes, polychromasia, and thrombocytopenia.

On the fourth hospital day, renal function worsened, with progressive elevation of the blood urea nitrogen and serum creatinine levels to 124 mg/dL and 10.3 mg/dL, respectively. The serum lipase level was further increased to 9609 U/L, serum amylase to 1257 U/L, and creatine kinase to 123,460 U/L. Urinalysis showed a large amount of blood but no erythrocytes. Results of liver function testing also became abnormal, with an increase of the serum aspartate aminotransferase level to 628 U/L and of the alanine aminotransferase level to 206 U/L (**Table 1**). The prothrombin time was 16 seconds (normal, 11–13 seconds), and activated partial prothrombin time was 38 seconds (normal, 29–36 seconds). Results of serologic testing for viral hepatitis were negative, and several blood cultures also were negative for microorganisms. The patient remained febrile, with a temperature as high as 38.8°C (102°F).

Diagnosis and Treatment

On the fifth hospital day, the diagnosis of TTP was established, based on the presence of MAHA, unexplained thrombocytopenia, and neurologic changes (specifically, mental status changes). Daily therapeutic exchange plasmapheresis using 3.5 L of fresh frozen plasma was immediately initiated. The patient became afebrile and regained mental alertness within 24 hours. After the fourth day of exchange plasmapheresis, the treatment was withheld, because the patient showed a marked clinical improvement with increasing platelet counts and hemoglobin level; creatine kinase level decreased to 30,000 U/L, blood urea nitrogen level to 43 mg/dL, and serum creatinine level to 2.7 mg/dL.

Four days later, however, the patient developed

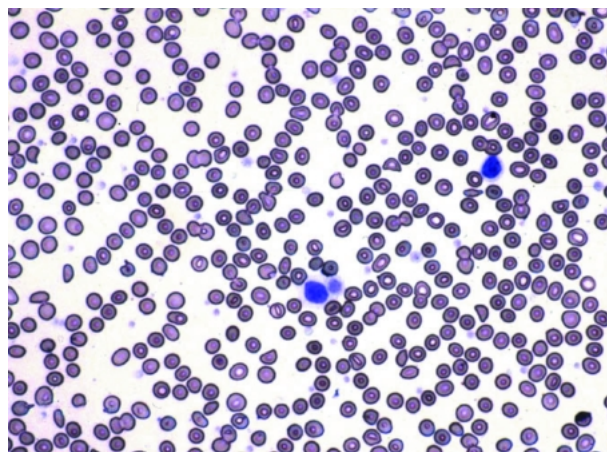


Figure 2. A peripheral blood smear from the case patient obtained after final exchange plasmapheresis showing normal erythrocytes and numerous platelets.

severe respiratory distress with increasing shortness of breath. He again became febrile (temperature to 39.4°C [103°F]). An arterial blood gas study showed a PO_2 of 43 mm Hg, a PCO_2 of 21.9 mm Hg, and an oxygen saturation of 80% while the patient breathed room air. Results of chest radiography were normal. Results of a ventilation-perfusion lung scan were also normal, with no evidence of pulmonary emboli. Severe generalized myalgia developed, and the patient became confused and disoriented. Creatine kinase level increased to 83,749 U/L. The urine was strongly positive for myoglobin. Exchange plasmapheresis was resumed.

On the 25th hospital day, after 10 additional plasma exchanges were performed, the patient achieved complete remission. He became alert and coherent. Hepatic, pancreatic, and muscle enzyme levels all returned to within normal range. Renal function, as manifested by blood urea nitrogen and serum creatinine levels, also returned to normal. The patient's respiratory distress disappeared, and oxygen saturation improved to 99% on room air. A follow-up peripheral blood smear showed normochromic, normocytic erythrocytes with fewer schistocytes and an adequate number of platelets (**Figure 2**). Twelve months after undergoing the last exchange plasmapheresis, the patient has no residual changes from his previous multiorgan failure and still remains in complete remission.

DISCUSSION

Multiorgan Involvement and Successful Plasmapheresis in the Case Patient

In the case patient, the diagnosis of TTP was well established, based on the findings of thrombocytopenia,

MAHA, and neurologic manifestations²; the presence of fever and renal failure further supported the diagnosis. In addition, atypical TM syndromes with multiorgan involvement, including involvement of the muscles (rhabdomyolysis), lungs (acute respiratory distress), pancreas (acute pancreatitis), and liver (acute hepatitis), were also present (Figure 3). This case illustrates and a review of the literature supports the contention that TM is indeed a multiorgan disorder, which may manifest as a variant form of atypical TTP. Although various presentations of TM, including acute respiratory distress syndrome,³ pancreatitis,^{10,11} and hepatitis, have been previously described, the fulminating rhabdomyolysis seen in the case patient is less common, having been reported only once before.¹² Additionally, unlike previously reported cases of TM syndromes, the case patient had simultaneous extensive multiorgan involvement and responded well to exchange plasmapheresis. Complete remission was achieved without any residual organ dysfunction.

Organs not involved our case, including the skin, eye, heart, and intestine, have been involved in cases of TM, although rarely.³⁻¹⁰ Undoubtedly, the rhabdomyolysis in the case patient was caused by TM, because it occurred in association with MAHA and thrombocytopenia, as well as other known TM syndromes, and responded promptly to exchange plasmapheresis. When the treatment was temporarily interrupted after an initial response, rhabdomyolysis recurred and responded again to the resumption of exchange plasmapheresis. We suspect that the rhabdomyolysis was caused by generalized muscle ischemia resulting from diffuse microthrombi in arteriolar capillaries of the muscle. Exchange plasmapheresis was promptly effective in the case patient, perhaps because the diagnosis was established at an early stage of the disorder and the fact that muscle is a highly regenerative organ, even after significant hypoxic injury.^{13,14}

Suggested Pathophysiology of Thrombotic Microangiopathy

Although hematologic features and pathologic changes of TM are similar to those of TTP and HUS, TM is a complex syndrome associated with diverse underlying pathologic conditions and undetermined pathogenic mechanisms. TM has been observed in association with administration of certain drugs,¹⁵ collagen vascular diseases,¹⁶ viral infections,¹⁷ pregnancy,¹⁸ and the postoperative recovery stage.^{19,20} In view of the close relationship between TM and various diseases involving the endothelium of blood vessels and the fact that endothelial injury results in release of unusually

Table 1. Laboratory Data for the Case Patient

Laboratory Parameter (normal values)	Prior to Exchange Plasmapheresis	After Exchange Plasmapheresis
Hemoglobin (14.5–16.5 g/dL)	8.6 g/dL	9.4 mg/dL
Platelets (150–450 × 10 ³ /mm ³)	13 × 10 ³ /mm ³	265 × 10 ³ /mm ³
Haptoglobin (26–185 mg/dL)	99 mg/dL	230 mg/dL
Reticulocyte count (0.5–1.5% of erythrocytes)	2.4%	2%
Serum lactate dehydrogenase (90–190 IU/L)	3052 U/L	253 U/L
Serum creatine kinase (38–174 mg/dL)	123,460 mg/dL	143 mg/dL
Serum lipase (10–140 U/L)	9609 U/L	85 U/L
Serum amylase (25–125 U/L)	1257 U/L	49 U/L
Serum aspartate aminotransferase (10–40 U/L)	628 U/L	83 U/L
Serum alanine aminotransferase (10–40 U/L)	206 U/L	71 U/L
Serum alkaline phosphatase (38–126 U/L)	85 U/L	79 U/L
Blood urea nitrogen (7–18 mg/dL)	124 mg/dL	20 mg/dL
Serum creatinine (0.6–1.2 mg/dL)	10.3 mg/dL	1.2 mg/dL
PO ₂ (80–100 mm Hg)	43 mm Hg	95 mm Hg
PCO ₂ (35–45 mm Hg)	21.9 mm Hg	43.7 mm Hg
Arterial oxygen saturation (92%–100%)	80%	100%

large von Willebrand factor (VWF) multimers, an endothelial pathology may play a key role in TM. Endothelial injury, due to either a disease process or a physical insult (eg, a surgical procedure), would release unusually large VWF multimers, which are known to cause platelet activation and aggregation if not cleaved to smaller multimers.

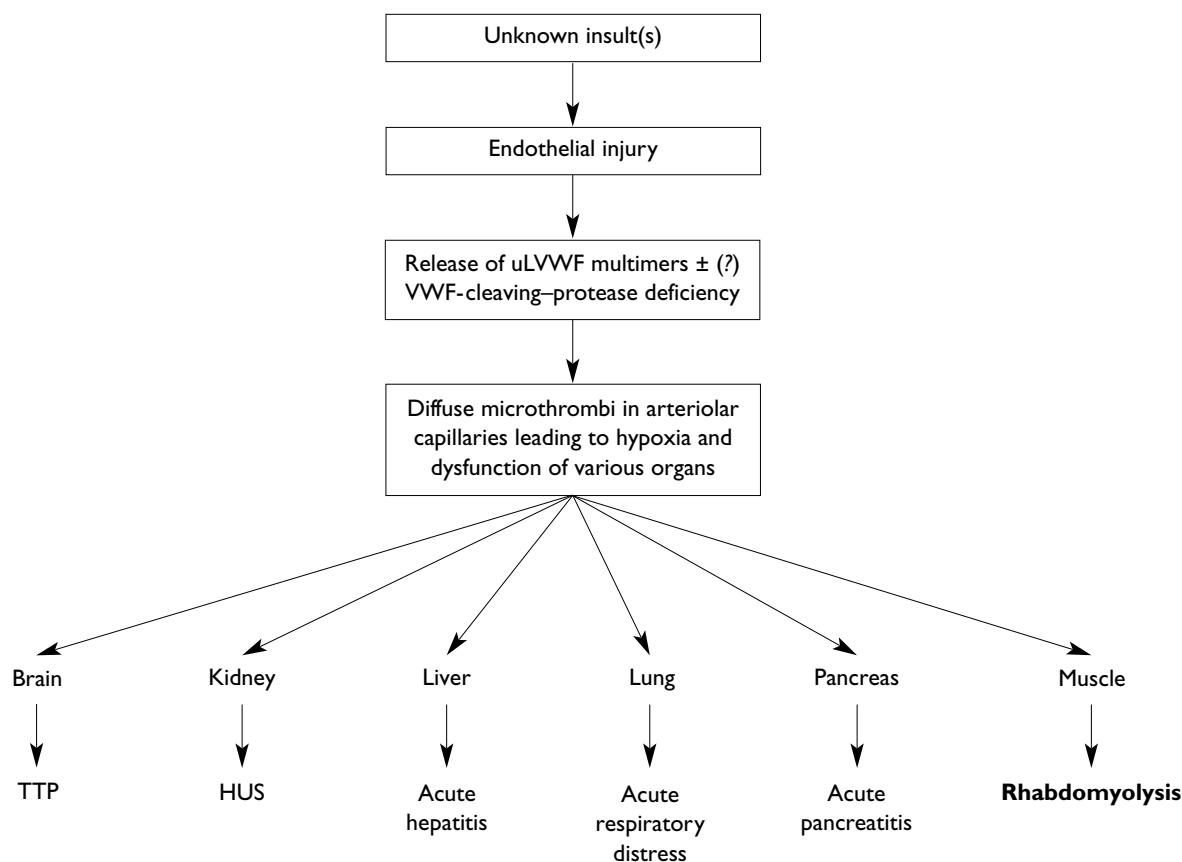


Figure 3. Proposed mechanism of thrombotic microangiopathic syndromes in the case patient. HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura; uLWVF = unusually large von Willebrand factor; VWF = von Willebrand factor.

Both a deficiency of a VWF-cleaving protease and the appearance of unusually large VWF multimers are found in patients with classic TTP.^{21,22} Because VWF-cleaving protease is responsible for the breakdown of unusually large VWF multimers into smaller multimers, the deficiency or inhibition of this protease (which may occur because of decreased production of the enzyme, antibodies against the protease, or interference with the activity of the protease) may lead to accumulation of unusually large VWF multimers.^{3,22} These multimers would promote platelet activation and aggregation in the arteriolar capillaries of various organs.²³

It is reasonable to suspect that a condition that causes an accumulation of large amounts of unusually large VWF multimers—either by an overwhelming release of these multimers because of extensive endothelial disease or injury, or by a lack of VWF-cleaving protease, or by a combination of both mechanisms—could trigger platelet aggregation in arteriolar capillaries and result in TM, at least in some patients. When this pathogenic

process extensively involves a particular organ, a unique TM syndrome such as acute rhabdomyolysis, as seen in the case patient, could develop as a result of muscle hypoxia caused by diffuse arteriolar microthrombi.²³ Classic and known atypical TM syndromes are shown in **Table 2**; involved organs and the clinical features of the syndrome are shown as well. MAHA is thought to occur as erythrocytes pass through shear-stressed arteriolar capillaries loaded by numerous platelet microthrombi.

Management of Thrombotic Microangiopathy

A critical aspect of the management of TM, especially when it presents as an atypical TM syndrome, is to establish the diagnosis at the earliest stage possible, because delayed or unrecognized diagnosis of is often fatal. Exchange plasmapheresis using fresh frozen plasma is an extracorporeal blood transfusion technique designed to remove large-molecular-weight substances from a patient's plasma. Currently, it is the primary therapy for TM; the goal is to remove 1 plasma volume

Table 2. Known Thrombotic Microangiopathic Syndromes*

Syndrome	Target Organ	Typical Clinical Features
Classic manifestations		
HELLP syndrome	Liver	Elevation of liver enzyme levels in association with pregnancy
Hemolytic uremic syndrome	Kidney	Renal failure
Thrombotic thrombocytopenic purpura	Brain	Central nervous system dysfunction
Atypical manifestations		
Acute respiratory distress syndrome	Lung	Respiratory distress
Hepatitis	Liver	Elevation of liver enzyme levels
Myocardial infarction	Heart	Chest pain, increased cardiac enzyme levels
Nonocclusive mesenteric ischemia	Intestine	Abdominal pain, nonthrombotic gangrene of the intestines
Pancreatitis	Pancreas	Abdominal pain, elevation of serum amylase and lipase levels
Peripheral digit ischemic syndrome	Digit	Gangrene, loss of fingers and toes
Retinal detachment	Eye	Visual loss or changes
Rhabdomyolysis	Muscle	Myalgia, elevation of creatine kinase level
Skin gangrene	Skin	Gangrene and ulcers

*Essential features are thrombocytopenia and microangiopathic hemolytic anemia with target organ involvement.

HELLP = hemolysis, elevated liver enzyme levels, and low platelet count in pregnancy.

per plasma exchange treatment and to replace the exchange volume with fresh frozen plasma. It is believed that the procedure replenishes the deficient VWF-cleaving protease and also may filter out the inhibitor of the protease. Additionally, the procedure may remove unusually large VWF multimers.^{23,24}

SUMMARY

Because TM is a hematologic emergency, its diagnosis should be considered in all patients with organ failure associated with unexplained thrombocytopenia and MAHA. In the case patient, exchange plasmapheresis was an effective treatment, causing a dramatic clinical improvement of all of the involved multiorgan dysfunction. The recovery was possible because of a high index of suspicion and timely treatment. In view of our experience, it should be emphasized that rhabdomyolysis can be another clinical manifestation of TM. This TM syndrome should be considered in any patient when evidence of muscle breakdown is associated with thrombocytopenia and MAHA, with or without the presence of other TM syndromes. **HP**

REFERENCES

1. Kwaan HC. Miscellaneous secondary thrombotic microangiopathy. *Semin Hematol* 1987;24:141–7.
2. George JN, Gilcher RO, Smith JW, et al. Thrombotic

thrombocytopenic purpura-hemolytic uremic syndrome: diagnosis and management. *J Clin Apheresis* 1998;13:120–5.

3. Chang JC, Aly ES. Acute respiratory distress syndrome as a major clinical manifestation of thrombotic thrombocytopenic purpura. *Am J Med Sci* 2001;321:124–8.
4. Podolsky SH, Zembowicz A, Schoen FJ, et al. Massive myocardial necrosis in thrombotic thrombocytopenic purpura: a case report and review of the literature. *Arch Pathol Lab Med* 1999;123:937–40.
5. Chang JC, Gupta S. Acute respiratory distress syndrome and non-occlusive mesenteric ischemia as major clinical manifestations of thrombotic thrombocytopenic purpura: Complete remission following exchange plasmapheresis. *J Clin Apheresis* 1998;13:190–2.
6. Luttgens WF. Thrombotic thrombocytopenic purpura with extensive hemorrhagic gangrene of the skin and subcutaneous tissue. *Ann Intern Med* 1957;46:1207–13.
7. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura: report of 16 cases and review of literature. *Medicine (Baltimore)* 1966;45:139–59.
8. Elias M, Flatau E, Bar-El Y. Thrombotic thrombocytopenic purpura presenting as an acute abdomen. *Br J Surg* 1985;72:286.
9. Panoskaltzis N, Derman MP, Perillo I, Brennan JK. Thrombotic thrombocytopenic purpura in pulmonary-renal syndromes [published erratum appears in *Am J Hematol* 2000;65:267]. *Am J Hematol* 2000;65:50–5.
10. Olsen H. Thrombotic thrombocytopenic purpura as a

- cause of pancreatitis. Report of a case and review of literature. *Am J Dig Dis* 1973;18:238–46
11. Jackson B, Files JC, Morrison FS, Scott-Conner CE. Thrombotic thrombocytopenic purpura and pancreatitis. *Am J Gastroenterol* 1989;84:667–9.
 12. Pena DR, Vaccarello M, Neiberger RE. Severe hemolytic uremic syndrome associated with rhabdomyolysis and insulin-dependent diabetes mellitus. *Child Nephrol Urol* 1991;11:223–7.
 13. Grossman RA, Hamilton RW, Morse BM, et al. Nontraumatic rhabdomyolysis and acute renal failure. *N Engl J Med* 1974;291:807–11.
 14. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982;61:141–52.
 15. Pisoni R, Ruggenenti P, Remuzzi G. Drug-induced thrombotic microangiopathy: incidence, prevention and management. *Drug Saf* 2001;24:491–501.
 16. Porta C, Caporali R, Montecucco C. Thrombotic thrombocytopenic purpura and autoimmunity: a tale of shadows and suspects. *Haematologica* 1999;84:260–9.
 17. Kelleher P, Severn A, Tomson C, et al. The haemolytic uraemic syndrome in patients with AIDS. *Genitourin Med* 1996;72(3):172–5.
 18. Burrows RF. Platelet disorders in pregnancy. *Curr Opin Obstet Gynecol* 2001;139:115–9.
 19. Chang JC, El-Tarabily M, Gupta S. Acute thrombotic thrombocytopenic purpura following abdominal surgeries: a report of three cases. *J Clin Apheresis* 2000;15:176–9.
 20. Chang JC. Review: Postoperative thrombocytopenia: with etiologic, diagnostic, and therapeutic consideration. *Am J Med Sci* 1996;311:96–105.
 21. Furlan M, Robles R, Galbusera M, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998;339:1578–84.
 22. Moake JL, McPherson PD. Abnormalities of von Willebrand factor multimers in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *Am J Med* 1989;87(3N):9N–15N.
 23. Chang JC, Kathula SK. Various clinical manifestations in patients with thrombotic microangiopathy. *J Invest Med* 2002;50:201–6.
 24. Lichtin AE, Schreiber AD, Hurwitz S, et al. Efficacy of intensive plasmapheresis in thrombotic thrombocytopenic purpura. *Arch Intern Med* 1987;147:2122–6.

Copyright 2003 by Turner White Communications Inc., Wayne, PA. All rights reserved.