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Various Clinical Manifestations in Patients with Thrombotic Microangiopathy

Jae C. Chang and Satheesh K. Kathula

ABSTRACT

Background: **Thrombotic microangiopathy (TM) is characterized by thrombocytopenia and microangiopathic hemolytic anemia in association with diffuse microthrombi in the arteriolar capillaries of various organs. Its clinical manifestation is protean, and a few well-defined clinical syndromes have been recognized. A clear understanding of the consequence of TM is needed to appreciate the unusual clinical syndromes due to atypical presentation of thrombotic thrombocytopenic purpura (TTP).**

Methods: **The medical records of patients with known diagnoses of TTP, hemolytic uremic syndrome (HUS), and the syndrome in which hemolysis, elevated liver enzymes, and low platelet count are found in association with pregnancy were examined retrospectively from 1981 to 1994 and prospectively from 1995 to 2000. Various thrombotic microangiopathic presentations were identified in these patients. Their response to exchange plasmapheresis was evaluated, and their clinical outcome was determined.**

Results: **A total of 74 patients were diagnosed with TM. Among these patients, several well-defined thrombotic microangiopathic presentations were identified. These presentations included TTP in 57 patients, acute respiratory distress syndrome (ARDS) in 13 patients, HUS in 9 patients, the syndrome in which hemolysis, elevated liver enzymes, and low platelet count are found in association with pregnancy in 9 patients, peripheral digit ischemic syndrome (PDIS) in 6 patients, pancreatitis in 3 patients, hepatitis in 3 patients, and nonocclusive mesenteric ischemia (NOMI) in 2 patients. Exchange plasmapheresis was an effective treatment, with a response rate of 79%. A poor prognosis was evident when ARDS was present, with an overall survival rate of 46%.**

Conclusion: **Traditionally, TTP and HUS are considered the main entities of TM. It is evident that other manifestations of TM, if unrecognized in a timely fashion, can lead to fatality. The understanding of the pathophysiologic consequences of TM and the recognition of its atypical presentations are essential to achieve favorable outcomes in patients with this life-threatening disease. (J Investig Med 2002;50: 201–206) Key Words: acute respiratory distress syndrome • hemolytic uremic syndrome • peripheral digit ischemic syndrome • thrombotic microangiopathy • thrombotic thrombocytopenic purpura**

INTRODUCTION

Although a classic clinical feature of thrombotic thrombocytopenic purpura (TTP) is the triadic presentation of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and neurologic manifestation, diagnosis of the dyadic presentation consisting of thrombocytopenia and MAHA is considered sufficient for timely management of the condition.[1] In addition, it is well recognized that TTP often presents with atypical clinical features, including pancreatitis,[2–3] cardiac dysfunction,[4–5] acute respiratory distress syndrome (ARDS),[6–7] acute abdomen,[8] skin gangrene,[9] and ocular manifestation.[10–11]

Recently, atypical cases of TTP have increasingly been recognized and treated with improved patient survival because of the availability of exchange plasmapheresis as an effective treatment and better correlation of clinical and pathologic findings.[12] In addition to both classic and atypical TTP, the term *thrombotic microangiopathy* (TM) has been proposed to encompass hemolytic uremic syndrome (HUS) and the syndrome in which hemolysis, elevated liver enzymes, and low platelet count are found in asso-

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ciation with pregnancy (HELLP syndrome).[13] The essential common features of these syndromes are thrombocytopenia and MAHA in association with diffuse microthrombi in the capillaries of various organs.[14]

In this study, we reviewed cases of TTP, HUS, and HELLP syndrome diagnosed in our institution. The diagnosis of TM was confirmed on the basis of the dyadic presentation of thrombocytopenia and MAHA. In addition to TTP, HUS, and HELLP syndrome, various thrombotic microangiopathic presentations are identified. The importance of recognizing these manifestations and the need for timely initiation of therapy are discussed.

PATIENTS AND METHODS

All identifiable cases of TTP, HUS, and HELLP syndrome seen at the Good Samaritan Hospital in Dayton, Ohio, were documented and recorded retrospectively in the personal computer system from 1981 to 1994. Also, these syndromes were recorded prospectively from 1995 to 2000. The essential diagnostic criteria of TM were unexplained thrombocytopenia (platelet count less than 100,000) and MAHA. Thrombocytopenia attributable to conditions such as blood transfusions, immune drug reactions, chemotherapy, infections, heparin-induced thrombocytopenia, consumption coagulopathy, and other conditions was excluded after pertinent clinical and laboratory evaluation in the differential diagnosis, as previously discussed.[15] The essential laboratory studies performed were prothrombin time, activated partial thromboplastin time, fibrin split products, and fibrinogen level, because these tests were indicated in almost all cases and the heparin-induced platelet aggregation test and ^{14}C serotonin release assay of the platelet when the tests had become available. Special attention was given to differentiating TM from heparin-induced thrombocytopenia according to previously published criteria,[16–17] because both conditions are often present with thrombotic thrombocytopenia. The diagnosis of MAHA was established unequivocally on the basis of brisk hemolysis with the demonstration of schistocytes in the peripheral blood film.[1] Hemolysis was confirmed by laboratory studies, including reticulocytosis, hypohaptoglobinemia, elevated lactic dehydrogenase level, and, if available, erythroid hyperplasia of the bone marrow on the aspiration and biopsy samples.

The clinical and laboratory data from these patients were reviewed and documented whenever possible to identify major clinical presentations caused by TM. These clinical presentations were identified when clear evidence of specific organ dysfunction was found, presumably caused by diffuse microthrombi in the arteriolar capillaries supplying the particular organ. Accordingly, fever alone was not considered to be an organ-related presentation, because it is presumed to be a systemic manifestation. Organ dysfunction due to identifiable causes such as diabetes mellitus resulting in renal failure, viral infection resulting in hepatitis, alcohol ingestion resulting in pancreatitis, and septic shock and pneumonia resulting in acute respiratory distress were excluded on the basis of clinical, laboratory, and radiographic studies. Because the review of 35 patients' medical records from 1981 to 1994 was retrospective, organ dysfunction that could not clearly be defined as a thrombotic microangiopathic presentation among these patients was excluded in this analysis.

The following major thrombotic microangiopathic presentations were identified: TTP (for brain involvement), HUS (kidney), HELLP syndrome (liver in association with pregnancy), ARDS (lung), peripheral digit ischemic syndrome (PDIS) (fingers and toes), nonocclusive mesenteric ischemia (NOMI) (intestines), acute pancreatitis (pancreas), and acute hepatitis (liver). The total number of patients demonstrating each presentation was tabulated. When more than one presentation occurred in a patient, each was counted as a separate presentation. Also, in each patient, the several identities of coexisting thrombotic microangiopathic presentation were determined.

In patients with ARDS, pancreatitis, and hepatitis, preexisting underlying pathology and clinical history were identified with regard to the respective organs to evaluate their contribution to these atypical manifestations. The mainstay of treatment, which was exchange plasmapheresis, was reviewed, and the final outcomes of patients with thrombotic microangiopathic presentations were recorded.

RESULTS

Seventy-four patients (35 patients in the retrospective study and 39 patients in the prospective study) met the essential diagnostic criteria for TM. As noted in Table 1, the patients ranged in age from 15 to 85 years (median age, 57 yr). The underlying pathology associated with TM was diverse. Idiopathic TM was seen in 31 patients, and secondary type was seen in 43 patients. The unusual finding was that in 22 patients, TM occurred in a postoperative setting. Pregnancies, malignancies, collagen vascular diseases, certain infections, and drugs were associated with the pathology in 21 patients.

Table 2 details the surgical procedures that resulted in TM and thrombotic microangiopathic presentations in 22 patients. In all of these patients, the review of medical records showed no clinical or hematologic evidence of TM before surgery. Clinical abnormalities, including thrombocytopenia and MAHA, usually occurred within 7 days after surgery. In these 22 patients with TM or thrombotic

Table 1. Patient characteristics.

Age (yr)	15–85 (median, 57)	
Race (no. of patients)		
Caucasian		48
African-American		25
Asian-American		1
Sex	27 men, 47 women	
Significant underlying pathology (no. of patients)		
None		31
Postsurgery		22
Pregnancy		9
Cancer		5
Breast cancer	4	
Stomach cancer	1	
Scleroderma		2
Legionella infection		2
HIV infection		2
Ticlopidine-induced		1

HIV, human immunodeficiency virus.

Table 2. Surgical procedures with thrombotic microangiopathic sequela.

Procedure	No. of Patients (n = 22)
Cardiovascular surgery	
Coronary artery bypass graft (CABG)	10
Non-CABG cardiac surgery	
Repair of foramen ovale	1
Resection of myocardial sarcoma	1
Aortic valve replacement	1
Pericardial window	1
Peripheral vascular surgery	
Femoropopliteal bypass graft	1
Aortopopliteal bypass graft	1
Arteriovenous fistula formation	1
Injured neck vessel repair	1
Gastrointestinal surgery	
Bowel resection	3
Cholecystectomy	1

microangiopathic presentations, the diagnosis of consumption coagulopathy and other acquired coagulopathy was ruled out on the basis of appropriate studies. None of these postoperative TM presentations was associated with the use of drugs (e.g., ticlopidine, quinine) that have been implicated in TTP. Interestingly, postoperative TM commonly developed in those patients who underwent cardiovascular or gastrointestinal operations. Among these patients, coronary artery bypass graft was the most common culprit with postoperative TM.

Table 3. Identifiable thrombotic microangiopathic presentations: Incidence and outcome.

Presentation	No. of Cases	Outcome (Alive/Death)
Thrombocytopenia and MAHA	2	2/0
TTP	57	37/20
ARDS	13	6/7
HUS	9	8/1
HELLP syndrome	9	9/0
PDIS	6	2/4
Pancreatitis	3	3/0
Hepatitis	3	3/0
NOMI	2	2/0

MAHA, microangiopathic hemolytic anemia; TTP, thrombotic thrombocytopenic purpura; ARDS, acute respiratory distress syndrome; HUS, hemolytic uremic syndrome; HELLP, hemolysis, elevated liver enzymes, low platelet count; PDIS, peripheral digit ischemic syndrome; NOMI, nonocclusive mesenteric ischemia.

Table 3 shows the total events and outcomes of patients with thrombotic microangiopathic presentations. Among all of the patients with TM, the combined diagnosis of thrombocytopenia and MAHA that was devoid of any obvious clinical manifestation due to organ involvement was present in two patients. One patient developed this syndrome after coronary artery bypass graft, and another was admitted to the hospital because of unexplained anemia and abdominal pain. By the time the hematologic consultation had taken place and the thrombocytopenia and MAHA diagnosis had been established, both patients were well on their way to spontaneous hematologic and clinical recovery. They achieved spontaneous remission and survived without specific treatment.

TTP due to brain involvement was the most common presentation of patients with TM. This syndrome was present in 57 patients. The next most common presentation was ARDS due to lung involvement, which was seen in 13 patients. HUS and HELLP syndrome were encountered in nine patients each. PDIS, not recognized as a presentation of TM, was seen in six patients; interestingly, all six of these patients developed PDIS in the postoperative setting.

Pancreatitis and hepatitis were seen in three patients each. NOMI was the major presentation in two patients.

Among 13 patients with ARDS, significant preexisting lung pathology was present in only one patient. The patient had had idiopathic unilateral pulmonary fibrosis for approximately 1 year. Four patients had coronary artery disease, and one patient had chronic renal failure. These diseases were considered not to be contributing factors in the patients' ARDS. The remaining seven patients had no underlying pathology that could cause compromised pulmonary function. None of the three patients with pancreatitis had any history of alcohol abuse or any history of pancreatitis. In fact, acute pancreatitis was the initial presentation of TM in one patient. Three patients with hepatitis also had no underlying liver disease or alcohol abuse before developing TM.

The number of patients with TM and their outcomes are recorded in Tables 3 and 4. Two patients with thrombocytopenia and MAHA had a good prognosis without treatment. Several treatment modalities had been tried in many patients. These therapies included steroids, antiplatelet agents, intravenous immunoglobulins, fresh frozen plasma, exchange plasmapheresis, renal dialysis, splenectomy, and cesarean section with termination of pregnancy in patients with HELLP syndrome. Sixty-two patients underwent exchange plasmapheresis. The number of exchange plasmapheresis procedures per patient ranged from 1 to 144. Among these treatments, exchange plasmapheresis was the most predictable and effective treatment for all patients, with the exception of patients with antepartum HELLP syndrome, in whom the treatment of choice was either induction or termination of the pregnancy. Exchange plasmapheresis resulted in a remission rate of 79%. In two patients with postpartum HELLP syndrome, exchange plasmapheresis was needed and was effective. Of the other 60 patients who were treated with exchange plasmapheresis, 49 patients responded and 44 patients survived.

The overall survival rate of patients with TM was 73%. The survival rate of patients with TTP was 65%, and that of patients with ARDS was 46%. The prognosis of patients with HELLP syndrome and HUS was excellent, with survival rates of 100 and 88%, respectively. Six patients had PDIS, which, when present, was associated with high (66%) mortality. All eight patients who had pancreatitis, hepatitis, and NOMI survived. Although 35 patients with TTP had no obvious organ involvement other than the brain, 22 patients with TTP had additional thrombotic microangiopathic presentations caused by other major organ involvement. The survival rate of TTP without other associated presenting conditions was 69%. It should be noted that the prognosis of TTP was considerably worse when ARDS also developed, in which case the survival rate was only 42%. All six patients with PDIS had TTP, and four patients had ARDS in addition. Of these six patients, four died.

Table 4. Outcomes of patients with thrombotic thrombocytopenic purpura without and with other thrombotic microangiopathic presentations.

Syndrome	No. of Cases	Outcome (Alive/Death)
TTP	35	24/11
TTP+ARDS	7	3/4
TTP+pancreatitis	3	3/0
TTP+HUS	2	2/0
TTP+PDIS	2	0/2
TTP+hepatitis	1	1/0
TTP+NOMI	1	1/0
TTP+ARDS+PDIS	3	1/2
TTP+ARDS+NOMI	1	1/0
TTP+ARDS+HUS	1	0/1
TTP+ARDS+PDIS+hepatitis	1	1/0

TTP, thrombotic thrombocytopenic purpura; ARDS, acute respiratory distress syndrome; HUS, hemolytic uremic syndrome; PDIS, peripheral digit ischemic syndrome; NOMI, nonocclusive mesenteric ischemia.

DISCUSSION

The laboratory consequences of TM are thrombocytopenia, which is likely due to in vivo platelet activation and aggregation, and MAHA that is characterized by red cell fragmentation caused by shear-stressed flow of the red cells in the area of microthrombi within the arteriolar capillaries.[18] Typically, a selected organ dysfunction due to ischemic changes manifests as TTP, HUS, or HELLP syndrome.[14] Until now, TM has been understood in the context of these three syndromes.[13] A review of our study and the literature makes it clear that, in addition to these three syndromes, there are other atypical but distinct clinical syndromes. These clinical entities include ARDS, PDIS, pancreatitis, hepatitis, and NOMI.[2–3,6–7,19–22] Although we have not identified other thrombotic microangiopathic presentations in our series, it is not surprising to find reports of involvement in the heart, skin, eye, and other organs.[4–5,9,10–11] Characteristic clinicopathologic features of TM are summarized in Table 5.

In some of our patients, ARDS, PDIS, pancreatitis, hepatitis, and NOMI were either the initial or a more prominent clinical manifestation of TM. Only later, after

Table 5. Characteristic clinicopathologic features of thrombotic microangiopathy.

Thrombocytopenia and microangiopathic hemolytic anemia
Diffuse microthrombi in the arteriolar capillaries
Progression to dysfunction in various organs due to diffuse ischemia
Lack of venous thrombi
Lack of grossly detectable thrombi, either arterial or venous
Mortality results if the diagnosis and treatment are delayed
Excellent response to exchange plasmapheresis

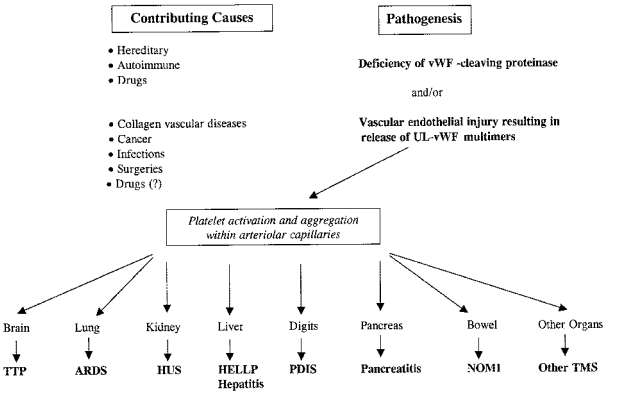

Figure 1. *Schematic of various presentations of patients with TM. vWF, von Willebrand factor; UL-vWF, unusually large von Willebrand factor; TTP, thrombotic thrombocytopenic purpura; ARDS, acute respiratory distress syndrome; HUS, hemolytic uremic syndrome; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count in association with pregnancy; PDIS, peripheral digit ischemic syndrome; NOMI, non-occlusive mesenteric ischemia; TMS, thrombotic microangiopathic syndrome.*

hematologic evaluation, could atypical TTP be diagnosed. The literature also contains reports of cases of pancreatitis that later were found to be associated with TTP.[2] Because some patients lacked the typical features of TTP at initial presentation or were masked, it is important to recognize that certain thrombotic microangiopathic presentations can occur without obvious features of brain involvement. An effective treatment for ARDS, pancreatitis, and NOMI caused by TM is exchange plasmapheresis in addition to treatment focusing on the control of infection, ventilation, and management of acute abdomen. If these presentations were overlooked, death would be a likely consequence even after an extensive, time-consuming evaluation and other treatments.

The neurologic manifestation of TTP and renal failure in patients with HUS is only one aspect of TM. For unidentified pathophysiologic reasons, arteriolar capillary thrombosis may occur predominantly in selected organs in a particular patient. Should diffuse microthrombi occur in the arteriolar capillaries of the lung, fingers and toes, pancreas, or mesenteries, the clinical syndrome would be ARDS, PDIS, pancreatitis, and NOMI, respectively (Fig 1). In our series, the presence of various thrombotic microangiopathic presentations and their effective response to exchange plasmapheresis confirmed the temporal relationship between TM and these presentations. We speculate that in patients with TM, all organs are affected. However, an underlying pathophysiologic condition or the severity of the disease in the particular organ may lead to clinical presentations of organ dysfunction that can be detected. A recent study showed that the pathogenesis of TTP seems to be somewhat different from that in HUS, because HUS usually lacks an inhibitor of von Willebrand factor multimer-cleaving proteinase, even though it has been detected more regularly in patients with classic TTP.[23]

In addition to the idiopathic type, TM has been observed with various underlying pathologies, including cancer, collagen vascular diseases, certain drug administration, and infectious diseases. Although we have seen various thrombotic microangiopathic presentations in both idiopathic and secondary TM, it should be noted that two presentations (ARDS and PDIS) commonly occurred in postoperative settings. Eight of 13 patients with ARDS and all 6 patients with PDIS developed the respective syndromes after surgery. In our series, 22 patients developed TM as a complication of surgery, which accounts for 30% of all patients with TM. This observation is unique because only a few reports have described TTP occurring as a result of surgery.[1,19,24] A possible explanation is that postoperative TM might have been overlooked, because this diagnosis is not usually made in a postoperative setting, and besides, we closely scrutinized almost every case of postoperative thrombocytopenia that occurred in our institution. Because in our series postoperative TM occurred after patients had undergone extensive operations involving blood vessels, our explanation is that damaged endothelial cells during the surgery could have released unusually large von Willebrand factor multimers that initiated platelet aggregation leading to TM.

Many postoperative complications can occur, including anemia, thrombocytopenia, mental changes, respiratory distress, renal failure, intestinal obstruction, and dehydration. These complications can often be blamed on anticipated transient postoperative events, and TM would not have a high index of suspicion as the cause of postoperative ARDS or other presentations. After cardiovascular or intestinal surgery in some of our patients, mechanical ventilation was needed during the postoperative recovery

period, and initially the development of ARDS and PDIS were presumed to be related to surgical events. The diagnosis of TM was not suspected until hematologic consultation was requested for an evaluation of unexplained thrombocytopenia and anemia.

Exchange plasmapheresis is the treatment of choice for TM.[25] Above all, the earliest possible treatment is critical because the thrombotic microangiopathic manifestation must be corrected before permanent organ damage occurs. In our patients with TM, the response rate to exchange plasmapheresis was 79%, and the survival rate of patients with TM was 73%. The review of our patients' records revealed two factors that were important prognostic determinants. First, the patient's prognosis was good if the diagnosis was established early and the treatment was initiated at the earliest possible time, especially in patients with TTP. Second, ARDS was associated with a poorer prognosis, probably because of delayed diagnosis and the serious nature of lung involvement. After the diagnosis of any of the spectrum of potential thrombotic microangiopathic presentations, the timely initiation of the management of TM is an important factor in achieving a favorable outcome for patients.

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