Thrombotic Microangiopathy: A Case Report and Review of the Literature

David L. Sommerfeld, Daniel C. Brennan, and Joel A. Gordon

A 26-year-old white woman (three pregnancies, three births, no abortions) was transferred to the University of Iowa Hospitals and Clinics 4 wk postpartum for the evaluation and management of acute renal failure. Her pregnancy had been complicated by mild proteinuria and hypertension, treated with methyldopa, during the last 3 wk of pregnancy. Her physical exam was remarkable for a blood pressure of 160/100 mm Hg, 1+ pedal edema, and hyperreflexia with 6 beats of clonus. Laboratory findings included sodium, 126 mEq/L (126 mmol/L); potassium, 4.4 mEq/L (4.4 mmol/L); chloride, 90 mEq/L (90 mmol/L); CO₂ content, 11 mEq/L (11 mmol/L); BUN, 170 mEq/L (6,017 mmol/L); creatinine, 24.8 mg/dL (2.192 μmol); total protein, 4.9 g/dL (49 g/L); albumin, 2.8 g/dL (28 g/L); calcium, 6.2 mg/dL (1.55 mmol/L); phosphorus, 16.4 mg/dL (5.30 mmol/L); and lactate dehydrogenase (LDH) 895 IU/L (14.92 mkat/L). A complete blood count showed a hemoglobin, 8.5 g/dL; and hematocrit, 26% (after 4 U of packed red blood cells [RBC] before transfer); platelets, 121 × 10³/mm³, and haptoglobin, <5 mg/dL (0.05 g/L). Schistocytes were seen on the peripheral smear. Direct and indirect Coombs tests were negative, prothrombin time was 13 s, and partial throm-
Thrombotic Microangiopathy

The patient required hemodialysis three times per week without ultrafiltration for control of uremic symptoms. On day six of her admission, she received 3 U of packed RBC and underwent suction curettage of the uterus for the persistence of heavy uterine bleeding. One week after completion of immunoglobulin G (IgG) treatment, schistocytes were no longer present on peripheral smear, platelets had risen sharply, and LDH normalized. She remained dialysis dependent until the 27th day after initial presentation, at which time her creatinine was 6.1 mg/dL (539.2 μmol/L). Forty-four days after initial presentation, a laboratory analysis showed hemoglobin, 9.0 g/dL; platelets, $319 \times 10^3$/mm$^3$; LDH, 196 IU/L (3.26 mkat/L); and creatinine, 3.9 mg/dL (344.8 mmol/L) (Figure 1).

On the 67th day after initial presentation, she complained of headache, fever, and fatigue, and laboratory findings revealed hemoglobin, 8.5 g/dL and platelets, $173 \times 10^3$/mm$^3$ with evidence of schistocytes on peripheral smear. LDH was 376 IU/L (6.27 mkat/L), and creatinine was 9.0 mg/dL (795.6 μmol/L). She was felt to have a recurrence of thrombotic microangiopathy and was treated again with high-dose IgG with prompt resolution of schistocytosis, increase of hemoglobin to 9.0 g/dL, and increase in platelets to approximately $250 \times 10^3$/mm$^3$ (Figure 1). Her urine output remained more than 2,500 mL/24 h, but because of significant reduction in her GFR, plasmapheresis and plasma exchange were initiated in an attempt to improve her renal status. After the institution of this therapy, urticaria developed, schistocytes returned, platelets decreased to $157 \times 10^3$/

**Figure 1.** Alterations in the patient’s serum creatinine concentration (top) and platelet count and hemoglobin concentration (bottom) during the first 100 days of her illness. The days of high-dose i.v. γ-globulin therapy (0.4 g/kg/day) are denoted by IgG. The days of plasma exchange therapy are indicated in the right half of both top and bottom portions. Hemodialysis treatments are denoted by the ↓ in the top portion of the figure on the days she received this therapy.
mm³, and hemoglobin decreased to 6.5 g/dL. Despite this, plasma exchange was continued three times per week empirically for 2 wk (Figure 1).

On day 22 after her second presentation, plasma exchange was discontinued and levels of hemoglobin and platelets rose (Figure 1). Her subsequent course was complicated by the development of non-A, non-B hepatitis. Six months after her initial presentation, a renal biopsy was performed showing chronic thrombotic microangiopathic changes affecting both glomeruli and vessels, consistent with prior thrombotic microangiography (Figure 2). After 3 yr of close follow-up, she has not had any further recurrences. Hypertension is controlled with enalapril, 5 mg twice daily, and her most recent serum creatinine level was 2.6 mg/dL.

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome are rare clinical entities characterized by platelet thrombi occluding the microvasculature. TTP was first described by Moschcowitz in 1924 when he reported the abrupt onset of fever, bleeding, hemolytic anemia, renal failure, and neurologic impairment in a 16-yr-old girl (1). Postmortem examination revealed hyaline thrombi in the terminal arterioles and capillaries, particularly in the heart, liver, and kidneys. The hyaline thrombi have since been determined to be composed primarily of agglutinated platelets and little fibrin (2). Hemolytic uremic syndrome was first described by Gasser et al. (3) in 1955 as a triad composed of acute renal failure, hemolytic anemia with schistocytosis, and thrombocytopenia. Historically, these two entities were distinguished by neurologic symptoms in the former and severe renal failure in the latter. In the adult, the overlap of these two syndromes can make them difficult to distinguish clinically. They have both been linked to similar precipitating factors, leading many to favor the notion that they actually represent different clinical expressions of the same disease that is currently referred to as thrombotic microangiopathy. In early reports, the mortality from thrombotic microangiopathy was nearly 100%. Since the advent of plasma therapy, effective treatment has approached 90% survival (4).

CLINICAL AND PATHOLOGICAL PRESENTATION

Thrombotic microangiopathy can occur in either sex at any age but has a peak incidence in women in their thirties. The childhood form of thrombotic microangiopathy differs in several respects from the adult form. In children, renal involvement is both more frequent and more severe. The mortality rate for children given only symptomatic treatment is less than 10% (5), a striking difference when compared with the 50% rate reported in adults (6).

Clinical presentation of patients with thrombotic microangiopathy can be quite variable, depending on the organ systems involved (Table 1). Often, a febrile prodrome with fatigue, abdominal pain, fever, nausea, and vomiting may be obtained in the history. Bleeding is a presenting feature nearly 85% of the time and may be manifested in the skin with petechiae or purpura, gross or microscopic hematuria, vaginal bleeding, or gastrointestinal bleeding (5). Nearly all patients will develop neurologic symptoms
such as headaches, paresthesias, confusion, seizures, or even coma as a presenting symptom or shortly after presentation. Renal involvement approaches 90% of patients and is usually manifested as hematuria and proteinuria (7). Elevations of serum urea nitrogen and creatinine are seen more frequently in severe cases and have even been implicated in predicting a poor outcome (7). Other organs such as lungs, pancreas, and heart are less frequently involved and may only be manifested through abnormal laboratory values.

Laboratory findings will invariably reflect a Coombs negative intravascular hemolytic anemia with elevated bilirubin and LDH, reticulocytosis, and low haptoglobin. RBC indices will usually be normochromic and normocytic, whereas a review of the peripheral blood smear will demonstrate schistocytes. Thrombocytopenia is found nearly 100% of the time with increased megakaryocytes on examination of the bone marrow. Coagulation studies are often normal, although prothrombin time and fibrin degradation products may be elevated.

The typical pathologic lesion in thrombotic microangiopathy is microvascular hyaline thrombosis, composed primarily of agglutinated platelets and little fibrin. These microvascular lesions can produce ischemic organ dysfunction in any tissue. It is predominantly manifested in those organs dependent on the microcirculation such as the brain, heart, pancreas, adrenals, and kidney. In the kidney, the microangiopathic changes may involve the glomerulus, the interlobular arteries, or both (7). Intravascular hemolysis and RBC fragmentation occur because of the mechanical damage of the RBC during their passage across fibrin strands in the damaged small vessels.

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of thrombotic microangiopathy have not yet been determined, although a number of conditions have been associated with the syndrome. In children, the clinical setting and occasional epidemic presentations suggest an infectious cause. Serologic evidence of Coxsackie virus, echovirus, and adenovirus infections have all been reported in children with thrombotic microangiopathy (6). Several cases have also been noted in children and adults after infections with Shigella, Salmonella, or Streptococcus species or Escherichia coli (6).

In adults, a wider variety of conditions have been associated with thrombotic microangiopathy. Several cases have been reported accompanying systemic diseases such as malignant hypertension, systemic lupus erythematosus, and scleroderma (6). A genetic predisposition has been suggested by several reports of relapsing thrombotic microangiopathy occurring in members of the same family (8). The disease has long been recognized in pregnant or postpartum females, along with women taking oral contraceptives. Finally, a number of drugs have been associated with the occurrence of thrombotic microangiopathy, especially cyclosporine and mitomycin (8).

The mechanism by which these various entities may cause thrombotic microangiopathy has not yet been established. One feature common to all of these clinical entities is that they injure vascular endothelial cells. Normally, the endothelium prevents thrombogenesis through several mechanisms. Endothelial cells secrete prostacyclin (prostaglandin I2 [PGI2]), which is the most potent substance known to inhibit platelet aggregation. In addition to the inhibition of platelet aggregation, PGI2 is an important antagonist of thromboxane A2, a potent vasoconstrictor. Endothelial cells also synthesize and secrete plasminogen activator, which dissolves thrombi by activating the proteolytic enzyme plasmin. Finally, endothelial cells synthesize, store, secrete, and process von Willebrand Factor (vWF), a glycoprotein that regulates platelet interaction with injured vessel walls. It has therefore been hypothesized that by inducing endo-
thelial cell damage, a cascade of events would ensue in the microcirculation, leading to the formation of thrombi and the clinical manifestations of the syndrome of thrombotic microangiopathy (6).

There are several theories as to the possible pathogenesis of thrombotic microangiopathy. They primarily focus upon (1) decreased production of endothelial cell PGI₂ or excessive lability of PGI₂ due to a deficiency of PGI₂-stimulating or -stabilizing factor present in normal plasma; (2) defective fibrinolysis due to inadequate production of endothelial cell plasminogen activator; (3) the presence of a substance capable of promoting intravascular platelet clumping; and (4) abnormal metabolism of vWF, multimers leading to increased platelet aggregation (8).

PGI₂ synthesis has been noted to be reduced in patients during active thrombotic microangiopathy (6). It has also been shown experimentally that endothelial cell damage stimulates rather than suppresses PGI₂ production (9), leading to the theory that PGI₂ synthesis is initially stimulated in the early phase of TTP and depressed later when more pronounced vascular damage takes place (6). It has also been demonstrated that patients with TTP lack a factor normally present in plasma that stimulates PGI₂ production (10). Despite this information about PGI₂, the infusion of PGI₂ has not been demonstrated as an effective therapeutic modality in thrombotic microangiopathy (8).

Plasminogen activator activity has been reported to be absent in vessels occluded by thrombi in patients with TTP but is present in normal amounts in uninvolved vessels in the same patient (11). It has therefore been suggested that local endothelial cell damage may inhibit plasminogen activator activity, decreasing fibrinolysis and potentiating thrombus generation. However, because fibrin formation is not necessary for the development of platelet thrombi, the role of decreased plasminogen activator activity and subsequent decreased fibrinolysis in the pathogenesis of thrombotic microangiopathy is unclear. Streptokinase infusion, which should increase fibrinolysis, has not been shown to be effective in the treatment of thrombotic microangiopathy (8).

The presence of a platelet-agglutinating factor has been detected in the plasma of some patients with active TTP (12). When mixed, plasma from patients with TTP has been shown to cause aggregation of platelets from normal donors. This agglutination is not inhibited by heparin, aspirin, antithrombin III, aprotase, or hirudin but could be abolished when incubated with normal plasma (10) and, more specifically, with normal human IgG (13).

Finally, unusually large vWF (ULvWF) multimers have been recovered from the plasma of patients with chronic relapsing thrombotic microangiopathy (14). These factors are much larger than those normally found in plasma and have an extraordinary ability to aggregate platelets (8). They are abundant in the circulation during remission and disappear during relapse, suggesting that some putative factor appears in the plasma, causes the unusually large vWF multimers to attach to platelets, and then causes them to aggregate. This aggregation can be blocked by the infusion of fresh frozen plasma, but not by albumin or IgG alone (8).

TREATMENT

Thrombotic microangiopathy in adults has been previously associated with a nearly 100% mortality rate. Because of the rapidly progressing fulminating course associated with the disease, various treatment modalities have been employed simultaneously. This makes it impossible to determine which treatment is specifically beneficial. Because of the poor outcome in untreated thrombotic microangiopathy, no placebo-controlled trials have been performed. Early recognition of this disease entity and supportive measures such as blood transfusion and hemodialysis are crucial for survival. The following summarizes the therapeutic modalities reported in the literature along with their rationale and efficacy (Table 2).

Supportive Measures

Much of the improved survival over the past three decades can be attributed to earlier recognition of the disease and efficient use of supportive measures. Many of the life-threatening symptoms such as electrolyte abnormalities and volume overload can be adequately controlled by hemodialysis. Severe anemia can be corrected through proper blood transfusions, and newer pharmacological agents allow better control of hypertension. Although these measures alone cannot account for the dramatic increase in patient survival, they allow time to implement the various therapeutic modalities listed below. They are

### TABLE 2. Therapeutic modalities used in thrombotic microangiopathy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response (%)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Exchange</td>
<td>80</td>
<td>16, 18</td>
</tr>
<tr>
<td>Plasma Infusion</td>
<td>60–70</td>
<td>16, 18</td>
</tr>
<tr>
<td>γ-Globulin</td>
<td>??</td>
<td>19</td>
</tr>
<tr>
<td>Vincristine</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>Antiplatelet Agents</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>11</td>
<td>4, 8, 16</td>
</tr>
</tbody>
</table>
also quite important for the long-term management of patients with residual end organ damage.

Plasma Therapy

Although four survivors were described after treatment with whole blood transfusion in Moschowitz’s original description of thrombotic microangiopathy in 1924 (1), this treatment modality was ignored until 1959 when Rubenstein et al. reported survival in a patient treated with exchange transfusions (15). Over the years, it has been demonstrated that normal plasma infusion, in combination with other agents, has been associated with improved recovery rates. Plasma exchange and plasma infusion have been reported to have 60 to 80% response rates and survival rates over 90% (16). Theoretically, plasma infusion supplies a factor deficient in patients with thrombotic microangiopathy. This missing factor could be an inhibitor of a platelet-activating factor, a substrate necessary for the formation of PGI₂, or a substance required for the normalization of VWF metabolism (17). Plasma exchange is efficacious in principle, because not only is the missing factor replenished but the toxic substances are also removed during the exchange procedure. A recent prospective trial comparing response in patients with thrombotic microangiopathy to antiplatelet agents and either plasma infusion or plasma exchange showed a 78% successful response rate to plasma exchange and only a 31% response rate to plasma infusion alone (18). Patients who failed to respond to plasma infusion initially and were subsequently treated with plasma exchange also achieved a high (78%) rate of response, suggesting exchange therapy is more effective than infusion alone. Many different schedules have been reported for plasma exchange, but most authors recommend an initial 7 days of therapy followed by alternate-day treatment until hematologic improvement. Recommended exchange volumes are 1 to 1.5 times the predicted plasma volume (18). Complications of plasma therapy include congestive heart failure and pulmonary edema if administered too fast, because renal insufficiency frequently accompanies this disorder. Long-term complications could include possible transmission of infectious agents such as non-A, non-B hepatitis as seen in this patient and, theoretically, exposure to the human immunodeficiency virus.

IgG

Recently, several case reports have appeared in the literature where i.v. γ-globulin was associated with remission of thrombotic microangiopathy (19). With the exception of the case reported here, all others were used in combination with other agents. The exact mode of action of high-dose γ-globulin is unclear, although it is based on the findings of Lian et al. that IgG inhibits the platelet-agglutinating factor present in patients with thrombotic microangiopathy (13). Its relative safety and suggested effectiveness have prompted several authors to suggest that controlled trials be performed (19). The current recommended dose is 0.5 mg/kg body wt/day given parenterally for 5 consecutive days. Although problems can still arise with volume management during IgG infusion, the risk of infectious complications is greatly reduced.

Vincristine

The vinca alkaloids are immunosuppressive agents that disrupt the polymerization of microtubules associated with platelet membranes. It has been used frequently in combination with other agents, especially in protracted cases, although response is often not as rapid as that typically seen with plasma therapy. Recommended dose is 2 mg i.v. initially followed by 1 mg i.v. every 4 days for 4 to 6 wk or for at least 2 wk after hematologic remission (20).

Splenectomy

Splenectomy has been used in several cases of relapsing thrombotic microangiopathy with variable results. A number of patients have achieved remission after the removal of the spleen. However, it has been argued that these patients also receive a significant number of blood products and dextrans during the procedure, which may account for its apparent efficacy. In a retrospective review of 92 patients receiving splenectomy in addition to various other agents, 51% achieved remission (16). Its use should be reserved for patients who fail to respond to other forms of therapy.

Glucocorticoids

Corticosteroids have been one of the earliest forms of therapy used in patients with thrombotic microangiopathy. In high doses, they have been shown to increase platelet survival in patients with thrombotic microangiopathy and other vasculitides (16). The hypothesized mode of action has been through the suppression of autoantibody production and the enhancement of suppressor T-lymphocyte activity. Their role is largely historical, and many authors now consider steroids ineffective.

Antiplatelet Agents

The possibility that thrombotic microangiopathy is manifested by diffuse platelet aggregation has led to the use of inhibitors of platelet function extensively over the past several years. Because of their frequent
use with other agents and the lack of controlled trials, their true efficacy remains unclear. Most authorities (4, 8, 16) do not advocate their use, because they are believed to be ineffective and because they tend to increase bleeding complications.

SUMMARY

Thrombotic microangiopathy most likely represents a spectrum of diseases consisting of multiple etiologies that has a final common pathway of multiorgan microvascular thrombosis. The variable responses to several different modes of therapy would suggest that more than one pathogenetic mechanism is involved. Untreated, it has been associated with very high morbidity and mortality rates. A poor understanding of the basic disease process has prevented specific treatment modalities, although early diagnosis and availability of dialysis and blood product transfusion services remain crucial. Several modes of therapy have been used to date, with plasma exchange being the most effective method studied and shown to improve survival. On the basis of current knowledge, this form of treatment should be instituted promptly in severe cases. Anecdotal reports of recovery with vincristine or IgG alone or with the use of IgG after the apparent failure of plasma therapy appear promising and deserve further investigation as initial therapeutic measures used in thrombotic microangiopathy. Although the majority of patients recover with normal renal function, those with severe thrombotic microangiopathy may heal through sclerosis with residual hypertension and chronic renal impairment requiring continual medical therapy.

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REFERENCES