

Attending Rounds: Microangiopathic Hemolytic Anemia with Renal Insufficiency

William F. Clark and Ainslie Hildebrand

Summary

The classification of thrombotic microangiopathy has evolved and expanded due to treatment and advances in understanding of the diseases associated with this clinical presentation. The three clinical forms of thrombotic microangiopathy—thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation—encompass a wide range of disorders that can be classified as either primary (idiopathic) or secondary to another identifiable disease or clinical context. Identification of an inhibitor to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) in the idiopathic and acute forms of TTP, recognition of the absence of ADAMTS13 inhibition in diarrheal HUS, identification of complement abnormalities in atypical HUS, and a better understanding of the role of plasma therapy, rituximab, and eculizumab therapy have all had a major effect on current understanding of the thrombotic microangiopathies. In this Attending Rounds, a patient with a thrombotic microangiopathy is presented, along with discussion highlighting the difficulty of differentiating TTP from HUS and disseminated intravascular coagulation, the need for a prompt diagnosis, and the role for plasma therapy in appropriately selected patients. The discussion attempts to provide a simple clinical approach to the diagnosis, treatment options, and future course of adults and children suffering from a thrombotic microangiopathy.

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Introduction

A previously healthy 35-year-old woman with no prior medical history presented to the hospital emergency department with a 5-day history of nausea, vomiting, and nonbloody diarrhea. She reported having a mild headache and feeling unwell but denied any other symptoms on detailed questioning. She had no recollection of experiencing similar symptoms previously. She lived with her husband and three children, all of whom had been exposed to a similar diet but did not have similar gastrointestinal symptoms. Her past medical history was unremarkable, with only the usual childhood illnesses and three normal full-term vaginal deliveries with no history of miscarriages. She indicated that her menstrual cycle was regular and she had no signs or symptoms of pregnancy. She was taking no medications, reported no unusual dietary habits, denied tobacco or drug use, and drank alcohol only occasionally. There was a family history of hypertension and dyslipidemia with ischemic heart disease but her two siblings and her three children were healthy.

On physical examination, mild pallor was noted and her vital signs were as follows: temperature, 98.0° F; heart rate, 90 beats per minute; respiratory rate, 16 breaths per minute; BP, 145/90 mmHg lying down and standing; and O₂ saturation, 98% on room air. She weighed 60 kg. Examination of her optic fundi revealed no hypertensive changes, her lungs were clear, her heart sounds were normal, her peripheral pulses were regular in both rate and amplitude, and her abdomen was diffusely tender on deep palpation without

specific localization or rebound tenderness. There was no edema and reflexes were brisk and symmetrical with no focal neurologic abnormalities detected.

Initial laboratory results revealed the following: plasma creatinine, 2.0 mg/dl; BUN, 36 mg/dl; hemoglobin, 9.0 g/dl; white blood cell count, $11.0 \times 10^9/L$; platelets, $40 \times 10^9/L$; and lactate dehydrogenase (LDH), 1800 U/L. Amylase, lipase, and liver function tests were normal. Urinalysis showed 1+ protein, >20 red blood cells/high power field, and >10 white blood cells/high power field with granular casts.

A tentative diagnosis of adult thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) was made on the basis of these presenting clinical and laboratory features. On further questioning, the patient denied eating undercooked beef products, ingesting unpasteurized milk or cheese, or having recent exposure to cattle. There was no history of kidney disease or family members that had a history of kidney disease, urinary tract infection, dysuria, frequency, fever, chills, or flank pain. The patient also had not experienced a prior history of oral or nasal ulceration, joint or pleuritic pain, or skin rash. On the basis of her initial test results, the patient underwent serologic testing and stool cultures for bacterial dysentery as well as blood and urine culture. Blood smear revealed normocytic red blood cells with schistocytes, occasional helmet cells, and a slight increase in reticulocytes. Her international normalized ratio was 1.1, partial thromboplastin time was 28 seconds, and D-dimer was <400 μg/L. The troponin

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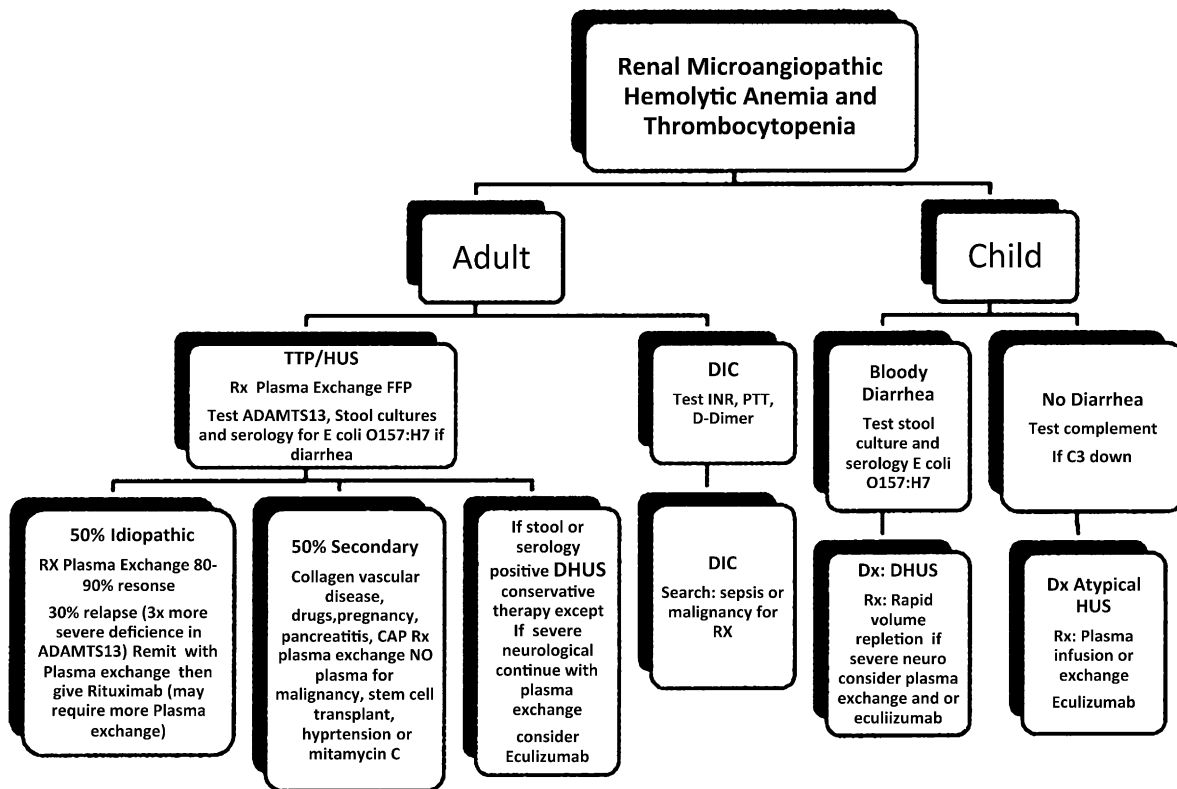


Figure 1. | Simple approach to thrombotic microangiopathy.

level was elevated at 0.12 $\mu\text{g/L}$. Blood samples were sent for determination of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) functional, antigenic, and inhibitor levels and to test for antiphospholipid antibodies.

Once the initial tentative diagnosis of adult TTP/HUS was made, treatment was immediately undertaken. Peripheral venous access was obtained, the patient was typed and crossed for 4.5 L of fresh frozen plasma, and after pretreatment with 100 mg methylprednisolone and 50 mg intravenous diphenhydramine underwent a 75 ml/kg plasma exchange with fresh frozen plasma. She subsequently demonstrated a dramatic response with a rapid clearing of her headache during the initial exchange and a rise in platelet count and decline in the LDH with daily plasma exchanges over the first 4 days. On day 5, before plasma exchange, her platelet count had dropped back to $140 \times 10^9/\text{L}$ after having risen to $180 \times 10^9/\text{L}$ on day 4, and her LDH, which had declined to 280 U/L, increased to 480 U/L. She also complained of a return of her headache and new onset of a transient episode of left-sided weakness lasting <10 minutes was noted.

The sudden change in direction of her response coupled with new neurologic findings prompted an increase in her plasma exchange volume to 150 ml/kg daily. The results of blood, urine, and sputum cultures were again negative. The increase in her plasma volume replacement resulted in a consistent increase in her platelet count and drop in her LDH. After receiving an additional 6 days of large volume plasma exchange, her platelet count reached $200 \times 10^9/\text{L}$

and her LDH was 110 U/L. She was entirely asymptomatic and her BUN and creatinine were 10 mg/dl and 1.0 mg/dl, respectively. Plasma exchange therapy was held and her response was monitored with daily LDH and platelet counts.

At this point, the ADAMTS13 assays requested at presentation returned revealing antigen and functional activity levels <5% of normal. An ADAMTS13 inhibitor was present compatible with a presumed diagnosis of idiopathic acute TTP. She was discharged with careful monitoring of her clinical status and platelet and LDH levels. She relapsed on day 21 postdischarge with a platelet count of $100 \times 10^9/\text{L}$ and LDH 360 U/L and was diagnosed as having early relapsing or refractory TTP. Plasma exchange therapy was reinitiated and once she was again in remission she was treated with rituximab 375 mg/m² weekly for 4 weeks. The patient received eight further plasma exchange treatments during her rituximab schedule to sustain her remission. She has since remained in complete remission for 2 years after her original presentation.

Discussion

In summary, this previously healthy woman presented with a 5-day history of nausea, vomiting, nonbloody diarrhea, malaise, and headache. Results of the patient’s preliminary blood work were consistent with a microangiopathic hemolytic anemia with thrombocytopenia and renal end-organ dysfunction. The fact that she was euvolemic on the basis of her vital signs favored renal end-organ damage

rather than intravascular volume depletion as the cause of her AKI. The clinical picture of a microangiopathic hemolytic anemia with thrombocytopenia indicated that she was suffering from a form of thrombotic microangiopathy associated with AKI. Figure 1 captures the clinical diagnostic approach to a patient presenting with a thrombotic microangiopathy. The three major diagnostic categories under consideration are HUS, TTP, and disseminated intravascular coagulation (DIC). Although it can be very difficult to differentiate DIC from HUS and TTP, the very low platelet count with normal international normalized ratio, partial thromboplastin time, and D-dimer in a patient with marked thrombocytopenia makes DIC less likely. Nonetheless, this remains a diagnostic possibility to revisit during the patient's course in view of recent reports from the Oklahoma TTP/HUS registry indicating that 7% of patients initially diagnosed with TTP were later confirmed to have DIC (1). Hence, it is important to culture blood and urine in a patient presenting with these clinical findings. An elevated white blood cell count, typical of infections, can be a feature of all three disorders, and thus does not aid in making a specific diagnosis of DIC.

The separation of TTP from HUS has major therapeutic implications. Mortality is >90% in untreated TTP, with most patients dying within 1–5 days of onset. In contrast, with plasma exchange therapy, survival is reported in >80% of patients (2). In addition, because there is no clear-cut evidence that diarrheal HUS (DHUS) related to infection with *Escherichia coli* O157:H7 benefits from plasma exchange (3), there is an urgent need to determine whether the patient has TTP or HUS secondary to *E. coli* O157:H7. Rare patients with atypical (nondiarrheal) HUS and hypocomplementemia have also been reported to benefit from plasma therapy. The mortality risk of plasma exchange therapy with thrombotic microangiopathy ranges from 0.03% to 2% (4). Much of the variability in this reported treatment-related mortality relates to both the nature of the reporting and the difficulty of separating events due to TTP/HUS from those due to plasma exchange.

I recommend treating most adults presenting with a renal thrombotic microangiopathy with thrombocytopenia and a normal coagulation profile as TTP/HUS with plasma exchange until the patient is proven to have DHUS by a positive stool culture or serology for *E. coli* O157:H7 (5–7). The patient presented above had thrombocytopenia, diarrhea, and kidney impairment compatible with the clinical diagnosis of HUS. Bloody diarrhea is seen in up to 70% of HUS patients but in only 6% of TTP patients. Among patients with TTP, up to 30% present with nausea, vomiting, and nonbloody diarrhea, as did this patient (8). Impaired kidney function is a major feature of HUS and is also seen in up to 60% of TTP patients (2,9). The absence of exposure to cattle or cattle by-products in our patient reduces the concern for DHUS. Hence, in this patient, initiation of plasma exchange was felt to be indicated once a tentative diagnosis of TTP/HUS was made while awaiting other laboratory test results. If our center did not have plasma exchange capabilities, we would have started plasma infusion (100 ml/h) and arranged prompt transfer to the closest plasma exchange center.

As in the patient presented here, the history and physical examination are used to initially determine if the patient has primary (idiopathic), hereditary, or secondary forms of

TTP/HUS (Figure 1). The patient had achieved adulthood and three full-term normal pregnancies without a prior hint of TTP/HUS, making the diagnosis of a hereditary form of TTP or atypical HUS less likely (10,11). In addition, she had no evidence of collagen vascular disease, she denied use of medications associated with TTP/HUS, and she clearly did not have pregnancy-associated TTP/HUS (12). She also had no history of prior clotting events or miscarriages as one might expect for someone suffering from a catastrophic antiphospholipid antibody syndrome presenting as TTP/HUS (13). Other potential causes of TTP/HUS, such as pancreatitis, disseminated malignancy, severe hypertension, or stem cell or bone marrow transplant, were not present (14–17).

This case presents several key issues of importance, such as the need for a simple approach to renal thrombotic microangiopathy to facilitate a timely diagnosis on the basis of simple signs, symptoms, and laboratory tests (Figure 1); the rapid application of specific therapy when a tentative diagnosis is made; and the importance of monitoring the course of therapy in order to alter the diagnosis and treatment when necessary. The exclusion of DIC secondary to infection or malignancy may not be entirely possible with negative screening tests and cultures at the time of admission, although a normal coagulation profile makes DIC much less likely (18). The lack of differentiation between TTP and HUS as a tentative initial diagnosis of TTP/HUS is to facilitate appropriate and timely treatment. Stool culture and serologies are often quickly available and thus helpful in excluding DHUS. ADAMTS13 test results, if abnormal, lead to a specific diagnosis of TTP rather than HUS in both adults and children. However, they are often not available in a timely fashion, and clinical suspicion and other laboratory characteristics thus must be carefully considered. ADAMTS13 testing is further limited by the observation that only a minority of patients with the clinical diagnosis of TTP who respond to therapeutic plasma exchange have a severe deficiency of ADAMTS13 with detectable antibody inhibitors (19). In our patient, a severe deficiency of ADAMTS13 and the presence of an inhibitor confirmed the diagnosis of TTP and also signaled that this patient had a three-fold greater risk of relapse after successful treatment than patients without severe ADAMTS13 deficiency (20). If our patient had not had an inhibitor to ADAMTS13 and severely reduced levels, we would have had to consider a diagnosis of atypical HUS. If this was the case and there was evidence of complement activation, genetic testing to identify a specific defect in complement regulation would be appropriate (21) and treatment with eculizumab might then be considered. However, the initial rapid rise in platelet count and drop in LDH level with clearing of clinical symptoms in our patient is much more in keeping with a diagnosis of acute TTP (9).

Our rapid escalation in the volume of plasma therapy on day 5 was predicated on the directional change in both platelet count (down) and LDH (up) with reappearance of neurologic symptoms (22). In general, a significant change in laboratory findings suggestive of disease recurrence even in the absence of new clinical manifestations would likely have prompted reinitiating plasma therapy; we would generally not resume plasma therapy in patients with new symptoms in the absence of some corroborating laboratory features.

There was an excellent response to the increase in plasma volume exchanged and she was declared to be in remission when she was asymptomatic with restoration of a normal platelet count after receiving a total of 10 plasma exchanges. Plasma therapy was held and regular laboratory monitoring revealed a continuing good response initially, but return of her headache and recurrence of thrombocytopenia with an increase in LDH signaled a relapse of her TTP. Because this occurred within 30 days of her remission, she was labeled as having a re-exacerbation or refractory TTP (23,24).

On the basis of this diagnosis, treatment with plasma exchange (150 ml/kg) was resumed until the patient was again asymptomatic and with a platelet count $>150 \times 10^9/L$ and the LDH was $<25\%$ above the normal range. At this point, treatment with rituximab was initiated. It is very important to induce a remission if possible with plasma exchange before introducing rituximab (given as four weekly dosages of 375 mg/m^2) because it may take 1–3 weeks for this drug to exert a therapeutic effect, during which time other severe manifestations of TTP—such as stroke, myocardial infarction, worsening kidney function, and even death—can develop if a plasma exchange-induced remission is not achieved (25). Because plasma exchange can remove rituximab, I try to hold exchange for 2 or more days after each dose if possible, whereas monitoring the patient closely for new signs, symptoms, or dramatic changes in platelet count or LDH that would dictate immediate plasma exchange rescue. Although there are good data from randomized controlled trials supporting the value of plasma exchange to treat TTP/HUS, we have to rely on anecdotal reports and a small randomized controlled trial in addressing the use of rituximab in treating refractory or relapsing forms of TTP/HUS, particularly in patients with severely deficient ADAMTS13 with inhibitors (2,26,27).

Finally, it should be noted that this patient had a slight elevation in troponin-I, which in the presence of a normal electrocardiogram and echocardiogram were thought to be compatible with mild transient cardiac ischemia secondary to TTP. Cardiac involvement has been noted to occur in up to 40% of patients with TTP and can be fatal (28). Cardiac and other systemic complications of a thrombotic microangiopathy, whether TTP or *E. coli* O157:H7-related HUS have both short-term and potential long-term consequences (29–31). In fact, the potential for increased cardiovascular disease in these patients who may have systemic microthrombosis secondary to the underlying thrombotic microangiopathy have led us to manage patients who have recovered from TTP/HUS as if they were at high cardiovascular disease risk with careful attention to BP control (target BP $\leq 130/80$ mmHg), use of dietary and lipid lowering therapy with statins to treat elevated LDL levels (target <100 mg/dl), and use of aspirin if not otherwise contraindicated.

Although the discussion above has focused on the diagnosis and therapy for adults presenting with renal microangiopathy, had our patient been a child with bloody diarrhea we would have treated him or her conservatively with careful volume repletion with a presumptive diagnosis of DHUS while awaiting results from stool and blood cultures and serologic studies (32). However, if the child developed serious neurologic signs and symptoms, we

would consider the use of plasma exchange, immunoadsorption treatment, and potentially eculizumab (33,34). Although plasma volume expansion has not been noted to be beneficial in the majority of children with DHUS, a meta-analysis did suggest the possibility of some benefit of plasma exchange in these patients (30). A recent outbreak of DHUS in Europe also suggests a potential major benefit for early plasma exchange therapy (35) and I do think it is reasonable to keep plasma therapy in the range of 50–75 ml/kg for at least 5 days as an option in the minority of children with HUS, particularly those whose neurologic syndrome is progressing after volume expansion. Recent evidence suggests that eculizumab 600 mg weekly for two doses may be of benefit in such patients who do not adequately respond to daily plasma exchange (33); the recommended dosing for atypical HUS delineated in the drug's US Food and Drug Administration–approved package insert is 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Further study is needed to more clearly define the risks and benefits of therapy, however, before it can be considered for standard practice in the treatment of patients with HUS. This drug is currently indicated for atypical HUS but not Shiga-toxin–related DHUS and its use in the United States requires enrollment of the prescribing physician in a Risk Evaluation and Mitigation Strategy program. Although no specific data are available, it does not seem likely that eculizumab will be cleared by dialysis. Use of eculizumab has been associated with severe meningococcal infection as well as infection with *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.

Final Diagnosis. Idiopathic thrombotic thrombocytopenic purpura.

Dr. Ainslie Hildebrand. Our patient did show red cell fragmentation at the time of presentation. Is that a necessary feature on which a tentative diagnosis and resultant plasma therapy is dependent?

Dr. Clark. No, it is not a necessary presenting feature since it may not be detected for 2–3 days on serial blood smear assessment but an elevated LDH would be a suitable early substitute (36).

Dr. Hildebrand. Is that because the LDH increase reflects hemolysis?

Dr. Clark. Initially, most investigators made that assumption but it has been shown by LDH fractionation the rise in LDH is due to fractions that reflect organ ischemia presumed to be due to microangiopathy rather than red cell hemolysis and hence the good correlation with drop in LDH and response to plasma therapy (37,38).

Dr. Gary Curhan. What are the role and risks of platelet transfusions in a patient with the tentative diagnosis of TTP/HUS?

Dr. Clark. I have not carried out platelet transfusions in the over 300 patients I have treated with the diagnosis of TTP/HUS but if the patient is bleeding platelet transfusions have not been shown to be harmful (39); but they have also not been demonstrated to be helpful.

Dr. Jeffrey Berns. How does one distinguish a patient with TTP with renal failure and severe hypertension from someone with severe hypertension and secondary renal failure with a microangiopathic hemolytic anemia?

Dr. Clark. It may be very difficult to distinguish in a minority of patients. Malignant hypertension is rarely associated with severe thrombocytopenia (platelet count $<20 \times 10^9/L$) and TTP is rarely associated with severe hypertension (diastolic BP >130 mmHg) (40). If the patient has severe hypertension and a platelet count $<20-50 \times 10^9/L$ I would initiate plasma exchange and aggressive BP control and await ADAMTS13 results. If the platelet count is $>50 \times 10^9/L$ and BP $>200/120$ mmHg, I would treat BP aggressively. If the platelet count and LDH worsen after good BP control or if ADAMTS13 is deficient, I would initiate plasma exchange (40).

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Disclosures

None.

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