A 32-Year-Old Woman With Chest Pain, Hematemesis, and Thrombocytopenia

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CASE PRESENTATION

A 32-year-old woman presented with a one day history of substernal, constant, non-radiating chest pain with associated abdominal discomfort, nausea, and vomiting of small amounts of blood of two days duration. She also reported headaches and dizziness during the day prior to presentation. Her past medical history was significant for hypertension treated with hydrochlorothiazide. The patient worked in a restaurant as a cook, smoked one-half pack of cigarettes daily, but did not use alcohol or illicit drugs. There were no recent sick contacts and the patient had no known allergies.

Physical examination revealed a heart rate of 100 beats per minute and a blood pressure of 115/72 mmHg. The patient was somnolent, but able to cooperate with the physical examination. The conjunctiva were pale and without icterus. She had several ecchymoses measuring 1-2 centimeters scattered on her legs and forehead. There were no focal neurologic deficits. Laboratory evaluation showed a hemoglobin of 7g/dL (12-16), hematocrit of 22% (35-46), a platelet count of 15,000/microliter (130,000-400,000), a serum creatinine of 1.3mg/dL (0.6-1.2), and a blood urea nitrogen of 19mg/dL (7-25). The prothrombin time was 12.5s (9.5-12.5), and the partial thromboplastin time was 25.8s (24-36). Serum haptoglobin was 11mg/dL (30-195); serum lactate dehydrogenase (LDH) was 1,600 U/L (30-195); serum lactate dehydrogenase (LDH) was 1,600 U/L (<201) with a total bilirubin of 2.5mg/dL (<1.3); indirect bilirubin was not available; and the direct Coombs was negative. The cardiac troponin was 1.85ng/mL (<0.09), and quantitative D-dimer level was 5,257ng/L (<231). Review of the peripheral blood smear revealed schistocytes (Figure 1). The findings of an elevated LDH, schistocytes, and cardiac ischemia were felt to be most consistent with a thrombotic microangiopathic hemolytic process, and a presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP) was made. The patient was emergently started on daily 1.5x plasma volume plasma exchange. Intravenous methylprednisolone was started at 1mg/kg for three days.

Twelve hours after the first plasma exchange the LDH dropped from 1,600 U/L to 479 U/L; cardiac troponin decreased to 0.34 ng/mL; platelets rose to 33,000/microliter; and total bilirubin dropped from 2.5mg/dL to 0.9mg/dL. After four additional plasma exchanges, the LDH had decreased to 254 U/L; hematocrit had risen to 31%; and platelets had normalized at 179,000/microliter (130-400). Schistocytes remained on the peripheral smear (Figure 2). The serum creatinine and total bilirubin remained normal at 1.2mg/dL and 0.8mg/dL, respectively. An ADAMTS13 enzyme activity from the time of admission returned one week later at 5% (>25%) and an ADAMTS13 inhibitor was positive at 0.5 inhibitor units (<0.4).

An echocardiogram was performed and revealed preserved left ventricular function with mild tricuspid regurgitation. Plasma exchange volumes were decreased to 1.0x plasma volume and tapered to every other day with no subjective or laboratory evidence for recurrent TTP over one week. At discharge, aspirin, 325mg orally daily, was started. Subsequent outpatient clinic visits showed continued remission. At one month follow-up, the LDH was 189...
U/L (<201); hematocrit, 36.5% (34%-46%); platelet count, 427,000/microliter (130-400); creatinine, 1.0 mg/dL (0.6-1.2); and a total bilirubin, 0.5 mg/dL (<1.3). Prednisone has been tapered to off, and her peripheral smear now demonstrates no schistocytes (Figure 3).

**DISCUSSION**

First described by Moschcowitz in 1924,1 thrombotic thrombocytopenic purpura (TTP) is a rare disorder often confused with other consumptive hematologic disorders such as disseminated intravascular coagulopathy (DIC), idiopathic thrombocytopenic purpura (ITP), HELLP (hemolysis, elevated liver enzymes and low platelets), and the hemolytic uremic syndrome (HUS) (Table 1). Historically, mortality with TTP exceeded 90%.2 With the use of plasma infusion or plasma exchange, the prognosis for TTP has improved significantly with long-term survivals now approaching 90%. Because of the implementation of effective treatments, empiric TTP therapy is often indicated even in unclear clinical situations with hemolysis, anemia, and thrombocytopenia.

The diagnostic pentad for TTP of thrombocytopenia, hemolytic anemia, renal failure, fever, and neurologic abnormalities was described 40 years ago.3 Since that time TTP has remained a clinical diagnosis though additional signs, symptoms, and laboratory findings have been suggested for inclusion as diagnostic criteria for TTP. For example, schistocytes on the peripheral smear are felt to be an essential condition for the diagnosis of TTP. This finding is not specific as blood from patients with malignant hypertension, pre-eclampsia, or mechanical heart valves, as well as from normal subjects, may have small numbers of schistocytes.4,5 The entire classic pentad is helpful, but not required, to make the diagnosis of TTP; clinical judgment remains the key.

Von Willebrand factor (VWF), a glycoprotein produced by platelets and endothelial cells, is integral to normal hemostasis, and it is essential for the formation of the initial platelet “plug” at sites of endothelial injury. VWF is produced as a large molecule referred to as the ultralarge VWF multimer (ULVWF) which has an enhanced ability to activate platelets. The ULVWF is cleaved by the metalloproteinase ADAMTS13 to the less active VWF. If ADAMTS13 activity is diminished, ULVWF is allowed to persist in the circulation. The resulting unimpeded platelet aggregation causes obstruction of capillary beds, widespread tissue hypoxia and schistocyte formation.

Idiopathic TTP is caused by inhibitory IgG antibodies directed against ADAMTS13, resulting in activities of approximately 5% of normal. As such, ADAMTS13 activity has been proposed as an additional component of the diagnostic pentad. However, this reduction in ADAMTS13 activity is not specific for TTP; it can be diminished in other hematologic disorders often confused with TTP such as systemic lupus erythematosus, immune thrombocytopenic purpura, and DIC. Further, the assay is often not rapidly available, and treatment should not be delayed if TTP is strongly suspected.

**TREATMENT**

Plasma contains small amounts of ADAMTS13 sufficient for normal hemostasis, and simple infusion of plasma can be used as initial treatment of TTP. Therapeutic plasma exchange (TPE) is more advantageous in that it allows both replacement of ADAMTS13 and removal of the antibody to ADAMTS13. TPE is performed by removing a patient’s plasma and replacing it with donor plasma, typically in the form of fresh frozen plasma (FFP). TPE is differentiated from apheresis (commonly used for organ transplant rejection or hyperviscosity syndrome) in which plasma is removed.
Table. Typical Findings in TTP, HUS, DIC, HELLP, ITP.

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<tr>
<th></th>
<th>TTP</th>
<th>HUS</th>
<th>DIC</th>
<th>HELLP</th>
<th>ITP</th>
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<tbody>
<tr>
<td>Bleeding</td>
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<td>None</td>
<td>Common</td>
<td>Rare</td>
<td>Petechial</td>
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<tr>
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<tr>
<td>Elevated LDH</td>
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TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic uremic syndrome; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzymes and low platelets; ITP = idiopathic thrombocytopenic purpura.

It is important to note that TPE is not a benign therapy; plasma is the critical component of TTP therapy. TPE results in long-term remission rates of 60%-80%.9

The superiority of TPE to simple plasma infusion was established by the Canadian Apheresis Study Group in which patients diagnosed with TTP received either daily plasma infusion or TPE. Patients were treated daily until the platelet count increased to 150,000/microliter and therapy intensity was reduced to five treatments given over two weeks. The TPE arm had higher initial response rates with a statistically superior overall survival of 78% versus 63%. Seventy-eight percent of patients treated on the TPE arm remained in remission at six-month follow-up.10

Remission of TTP is loosely defined and can be a source of debate for when to stop intensive therapeutic interventions. Remission is usually defined as resolution of thrombocytopenia, a normalization of serum LDH, a stable hemoglobin, resolved neurologic deficits, and normalized renal function. (Schistocytes may remain on the peripheral smear even when other laboratory parameters have normalized.) Once these laboratory endpoints have been reached, TPE may be stopped or tapered to every other day initially. For the most part, the decision to withdraw therapy requires a thorough and constant evaluation of the entire clinical and laboratory data. If a patient experiences a relapse after stopping TPE, therapy needs to be resumed.

It is important to note that TPE is not a benign therapy; patients require an indwelling central venous catheter; the exchange process is associated with hypocalcemia and volume shifts; and patients are exposed to blood products derived from multiple donors. A recent review of patients treated with TPE showed that one-quarter developed hypotension, bacteremia, or deep vein thrombosis with a 2% incidence of treatment-related deaths.11 Expert opinion supports continuing daily TPE for a few days, typically 2-3, after remission is achieved as “consolidation.” The decision to continue TPE needs to be balanced against the potential complications.12

Cryoprecipitate-poor plasma (CPP) is a plasma product that is deficient in the large VWF multimers that play the key role in the pathophysiology of TTP. It has been proposed that CPP may be superior to FFP due to lack of these multimers. One small randomized, prospective trial performed by the North American TTP Group directly compared FFP to CPP as initial therapy for TTP. There were no differences reported in overall survival or response rates.13 Despite lack of efficacy in upfront therapy, CPP has been demonstrated to be effective in the salvage setting after failure with FFP.14,15

The addition of corticosteroids to TPE may result in a more durable remission of TTP ostensibly by suppressing production of antibodies directed against ADAMTS13.16 As an example, one series has reported treating patients diagnosed with TTP with 200mg of prednisone per day only. Fifty-one percent of patients achieved a durable remission despite withholding TPE and plasma infusion.17 (We would caution that employing plasma infusion/exchange is currently the accepted standard of care.) The Canadian Apheresis Study Group trial, described previously, did not use steroids and had outcomes similar to other reported exchange trials with steroid containing treatment arms. Expert opinion recommends that steroids can be added when response to TPE alone is poor.18 Short pulses of 1 gram methylprednisolone daily for three days can be used at the time of diagnosis concurrent with TPE in order to limit long-term steroid exposure. Steroid therapy should also be considered in emergent situations where TPE or plasma infusions are not immediately available.

Platelet adhesion onto VWF multimers serves as the cause of the development of microvascular thrombosis. Some researchers have proposed blocking additional platelet aggregation with the use of aspirin or aspirin containing compounds. While aspirin acts as a potent inhibitor of platelet aggregation not directly associated with TTP pathophysiology (through inhibition of thromboxane-dependent pathways), early clinical research suggested that...
antiplatelet agents helped achieve disease remission. Many later study protocols evaluating TPE for TTP have included platelet inhibitors such as aspirin and/or dipyridamole, Recently, a small prospective trial that directly compared TPE to TPE/aspirin, and there was no difference in remission rates or numbers of death. In addition, fatal hemorrhage is of concern when using platelet inhibitors with concomitant thrombocytopenia. Prospective data show approximately 8% of patients will experience bleeding complications while on aspirin and TPE, but none of these episodes result in death or interfere with TTP therapy. As most clinical trials evaluating TPE have included aspirin, many practitioners consider its use a standard component of therapy. A consensus conference has suggested starting aspirin when the platelet count is greater than 50,000/microliter.

OTHER ETIOLOGIES OF TTP

Microangiopathic hemolytic anemias of various etiologies can present with clinical features that are similar to classic TTP. These scenarios include systemic lupus erythematosus (SLE), pregnancy, and a TTP syndrome induced by various drugs or stem cell transplantation. Even though these TTP-like syndromes resemble idiopathic TTP in all laboratory and clinical parameters, standard therapies are not always of clear benefit.

The association of TTP with SLE has been frequently reported in the medical literature. Simultaneous development of these two diseases likely stems from overlapping autoimmune processes, and distinguishing TTP from SLE can often prove difficult. Active lupus may present with the classic pentad seen in active TTP and often does so. In one large case series of patients with TTP and SLE, treatment consisted of either TPE, plasma infusion, steroids, or no TTP directed therapy. The overall mortality was relatively high (34%) despite the use of aggressive interventions. Specifically, the mortality rate even with TPE was 32%.

TTP occurring during pregnancy can be confused with the HELLP syndrome or pre-eclampsia; often the distinction is impossible to make. Potential complications from TTP include death of the mother or loss of the fetus by placental infarction. Most practitioners recommend delivery of a viable fetus, as delivery will result in resolution of pre-eclampsia and HELLP. Elective termination of non-viable fetus or early delivery is not necessary when TTP is strongly suspected. Instead, standard therapies should be employed until remission or until delivery is feasible.

TTP associated with commonly used drugs is described extensively in the literature; quinine, ticlopidine and mitomycin-C are most frequently implicated. The pathophysiology of drug-induced TTP differs from idiopathic TTP in that most cases associated with drugs do not have an ADAMTS13 inhibitor. Withdrawal of the offending drug should be the first therapeutic intervention but standard therapies such as TPE should also be implemented. Drug-induced TTP is associated with a high mortality rate. For example, quinine-associated TTP treated with plasma exchange has a 21% mortality rate, and ticlopidine-associated TTP has an overall mortality of 18%. TTP induced by mitomycin C (now used almost exclusively in the therapy of anal canal carcinoma) has been treated with TPE, plasma infusion, or glucocorticosteroids, in various combinations; survival rates range from 0%-25%. As it relates to mitomycin C, the high mortality rate stems, in part, from the poor prognosis of the underlying malignancy for which the drug was used.

Stem cell transplant is employed for the cure of many hematologic malignancies and is often associated with microangiopathic anemia, thrombocytopenia, fever, neurologic pathology, and renal failure, ie, signs and symptoms routinely seen in the transplant setting and not necessarily indicative of TTP. Patients with transplant-related TTP usually have normal level of ADAMTS13. Instead, the underlying mechanism of the microangiopathic process is felt to be directly related to endothelial damage from myeloablative chemotherapy. The incidence of TTP associated with transplant is reported to range between 2%-76%. The largest series describing this disorder reports an 18% response rate to TPE, with a 42-month overall survival of 6%. Patients who develop this TTP syndrome in the transplant setting do poorly, and TPE is likely of limited utility.

A rare congenital form of TTP, referred to as chronic relapsing TTP, typically presents in infancy or early...
adulthood with episodes occurring at 3-4 week intervals. It is inherited in an autosomal recessive manner. Deficient ADAMTS13 activity results from missense mutations in the gene encoding ADAMTS13. The course of the disease is variable with patients often requiring simple plasma infusions monthly; plasma exchange does not have a role in treating this disorder. Patients who present for the first time in adulthood typically have long asymptomatic periods and require only intermittent plasma therapy.

**DEVELOPING THERAPIES**

As noted previously, immunosuppressive therapies such as glucocorticoids are used with TPE as part of either upfront therapy or with refractory disease. Rituximab (Rituxan®) is an anti-CD20 antibody used in the treatment of B-cell lymphoproliferative disorders that also has immunosuppressive properties. Rituximab has been used in an off-label manner in cases of TTP refractory to TPE, and published case series all report a clinically significant response to rituximab, with low relapse rates of approximately 14%. The actual efficacy of rituximab is likely obscured by the concomitant use of other agents in these non-controlled studies. Given the promising early data for rituximab, a randomized trial is being implemented to determine whether rituximab given early in the course of treatment reduces the need for TPE and reduces relapse rates.

**SUMMARY**

The diagnosis of TTP should be considered in any clinical scenario in which hemolysis and thrombocytopenia are present. If other secondary causes are ruled out, therapy should instituted as rapidly as possible. TPE remains the standard of care for TTP. In emergent situations where TPE is not immediately available, infusion of FFP at 15 mL/kg per day and initiation of glucocorticoids is acceptable.

**REFERENCES**


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