

Thrombotic thrombocytopenic purpura masquerading as a stroke in a young man

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A 40-year-old previously well man presented to an urgent care centre after the rapid onset of dysarthria and unilateral arm weakness. The symptoms resolved over 15 minutes. There were no atherosclerotic risk factors, and he did not report other signs. On examination, his vital signs were within normal limits, and there were no focal neurologic signs, icterus, petechiae, lymphadenopathy or hepatosplenomegaly. A complete blood count showed normochromic normocytic anemia, with a hemoglobin level of 100 (normal 137–180) g/L, leukocyte count of 6.9 (normal 4.0 – 11.0) $\times 10^9$ /L and platelet count of 23 (normal 150 – 400) $\times 10^9$ /L. Computed tomographic angiography of the brain showed no stroke or vascular anomalies. After telephone consultation with a stroke neurologist, the patient was discharged, to be followed in 36 hours at a stroke assessment clinic. A smear for schistocytes was automatically ordered; however, the result was not available at discharge.

The day of his follow-up appointment, the patient became confused. Assessment in an emergency department showed disorientation, scleral icterus and bruising to the extremities. His hemoglobin level was 99 g/L, leukocyte count 6.0×10^9 /L, platelet count 23×10^9 /L, serum lactate dehydrogenase level 807 (normal 100–235) U/L, serum total bilirubin level 95 (normal 0–24) μ mol/L, reticulocyte count 6.6% (normal 0.2%–2.0%) and serum haptoglobin level less than 0.15 (normal 0.30–2.00) g/L. A peripheral blood smear showed schistocytes. Hematology and the plasmapheresis services were consulted. A preliminary diagnosis of thrombotic thrombocytopenic purpura (TTP) was made.

The patient was admitted and received emergent daily therapeutic plasma exchanges with fresh frozen plasma and oral prednisone treatment (1 mg/kg per day). His ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was very low (0.81% [normal 40.00%–130.00%]), and his ADAMTS-13 antibody level was elevated (106.52 units/mL), consistent with acquired TTP. His platelet count recovered rapidly, and his serum lactate dehydrogenase level decreased (Figure 1). Thromboprophylaxis was started once the platelet count was greater than 50×10^9 /L.

On day 7, the patient's laboratory values worsened. Therapeutic plasma exchanges were reinitiated, and the patient was

KEY POINTS

- Thrombotic microangiopathy due to thrombotic thrombocytopenia should be suspected in a patient with otherwise unexplained thrombocytopenia and anemia, even without fever, renal dysfunction or neurologic symptoms.
- Evaluation for anemia and thrombocytopenia should include an emergent peripheral blood smear to look for schistocytes, indicative of microscopic hemolytic anemia.
- A patient with suspected thrombotic thrombocytopenic purpura (TTP) requires emergent management with therapeutic plasma exchanges; referral should not be delayed while the diagnosis is being confirmed.
- Plasma infusion can be used as a bridge while the patient is being transferred for definitive therapeutic plasma exchange.
- Unless there is life-threatening bleeding, platelet transfusions are absolutely contraindicated in TTP, as the platelets will cause further microvascular thrombosis and end-organ damage.

treated with rituximab (375 mg/m² given intravenously). Over the next 72 hours, he experienced anxiety and intermittent chest pain. An electrocardiogram was normal, but his serum troponin T level was elevated, at 1076 (normal 0–14) ng/L, and the platelet count was 12×10^9 /L. He experienced a sudden decrease in his level of consciousness associated with hypotension and severe lactic acidosis (serum lactate level 13.6 [normal 0–2.0] mmol/L). Investigations for pulmonary embolism gave negative results. The patient died from nonsupportable shock about 10 hours later, 9 days after hospital arrival and 11 days after the appearance of his first symptoms. He did not receive platelet transfusions during his hospital stay. A patient safety review was conducted.

Discussion

Thrombotic thrombocytopenic purpura is one of a relatively uncommon but potentially life-threatening group of hematologic emergencies known as thrombotic microangiopathies.¹ Thrombotic microangiopathies occur because of abnormal platelet aggregation and resultant thrombi formation in small blood vessels, potentially resulting in end-organ injury in the brain, kidney,

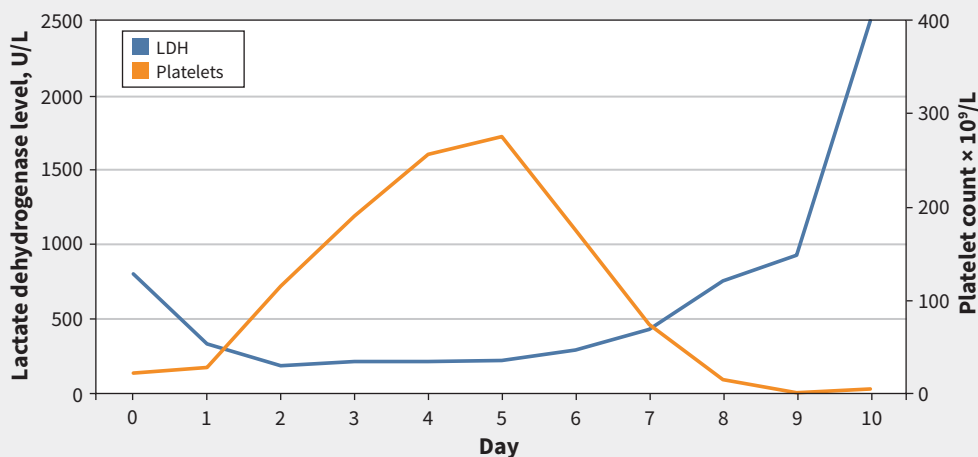


Figure 1: Progression of platelet count and serum lactate dehydrogenase (LDH) level during course of illness.

heart and gastrointestinal tract. They are characterized by microscopic hemolytic anemia with thrombocytopenia. Symptoms may include jaundice, icterus, petechiae, bruising, fever, neurologic changes or headache, and oligoanuria. Biochemical abnormalities include elevated serum bilirubin and lactate dehydrogenase levels, elevated reticulocyte count and decreased serum haptoglobin level. The microscopic hallmark of thrombotic microangiopathy is polychromasia with erythrocyte destruction or fragmentation.¹

Thrombotic microangiopathies include several distinct conditions (Box 1) such as hemolytic uremic syndrome, the most common thrombotic microangiopathy in children, which is caused by Shiga toxin secreted most commonly by specific *Escherichia coli* strains or, occasionally, other bacteria.² Hemolytic uremic syndrome from Shiga-toxin-producing *E. coli* presents with a prodrome of diarrhea, renal failure and, less commonly, neurologic symptoms. Diarrhea may also occur in other thrombotic microangiopathies. Atypical hemolytic uremic syndrome is usually a genetic disease arising from uncontrolled activation of the alternative complement cascade, which leads to uncontrolled production of C5b-9 (membrane attack complex), causing microvascular endothelial damage.² Disseminated intravascular coagulation may arise from emergent and life-threatening shock or as a subacute manifestation of other conditions (e.g., cancer). Thrombotic microangiopathies may also be associated with other conditions including pregnancy or the postpartum period, malignant hypertension, exposure to certain drugs (gemcitabine, ticlopidine, quinine, valacyclovir, cyclosporin and illicit cocaine), malignant disease and connective tissue disorders.³

Determining whether there is a secondary thrombotic microangiopathy or whether the associated condition has triggered an underlying complement dysregulation (atypical hemolytic uremic syndrome) should be done in conjunction with experts in the area. In addition, congenital variants of thrombotic microangiopathy are often clinically unapparent until triggered and are an important consideration in adults.¹

The hallmark of TTP is severely reduced ADAMTS-13 activity.¹ Endothelial cells release ultralarge multimers of von Willebrand factor, which contributes to the aggregation of platelets to sites of endothelial injury, resulting in the formation of platelet-rich thrombi. ADAMTS-13 cleaves the bonds of ultralarge multimers of von Willebrand factor, thereby regulating it. In severe ADAMTS-13 deficiency, there is accumulation of ultralarge multimers of von Willebrand factor, which results in the development of platelet-rich microthrombi in arterioles and capillaries. This condition can be congenital (mutations in the encoding gene) or, more commonly, acquired as a form of autoimmune disease with antibodies directed against ADAMTS-13.⁴ Autoimmune TTP is commonly associated with triggers, such as infections, pregnancy and other autoimmune conditions.⁶

Diagnosis

Classically, TTP has been associated with a pentad of symptoms: microscopic hemolytic anemia, thrombocytopenia, fever, renal failure and neurologic symptoms. However, the full pentad is present in less than 10% of cases.⁷ The presence of unexplained anemia and thrombocytopenia should prompt microscopic examination of erythrocytes in a peripheral blood smear to identify microscopic hemolytic anemia through the presence of schistocytes. Once the diagnosis of TTP is suspected, emergent therapy is necessary.³ The hematologic markers are sufficient to initiate the critical steps of consulting a hematologist and transferring care to a facility with the ability to provide therapeutic plasma exchange. Patients and families should be informed that this is a life-threatening condition. Thrombotic thrombocytopenic purpura may progress rapidly, and, without appropriate therapy, mortality rates approach 100%.^{1,3} With rapid effective therapy (therapeutic plasma exchange and immune suppression), mortality rates are 10%.^{3,6} Therapy should not be delayed for confirmation of ADAMTS-13 levels or to exclude another cause of thrombotic microangiopathy.

Box 1: Potential causes of thrombotic microangiopathy in adults and some of the hallmarks of these conditions¹⁻⁵

Cause	Hallmark(s) of disease
Thrombotic thrombocytopenic purpura	Severe ADAMTS13 deficiency Autoimmune or genetic
Atypical hemolytic uremic syndrome	No clear diagnostic test in acute setting Genetic or autoimmune dysregulation of alternative complement cascade
Hemolytic uremic syndrome	Positive result of polymerase chain reaction testing of stool for Shiga toxin More common in children
Disseminated intravascular coagulation	Elevated international normalized ratio/partial thromboplastin time, low fibrinogen level Patient is often critically ill
Medication/drug induced	Calcineurin inhibitors (cyclosporin, tacrolimus), gemcitabine, valacyclovir, quinine, ticlopidine, illicit cocaine
Malignant hypertension	–
Pregnancy	Manifestation may relate to duration of pregnancy Difficult to distinguish from HELLP syndrome; liver enzyme tests may be helpful
Malignant disease	Often disseminated cancer
Systemic autoimmune disorders	
Systemic lupus erythematosus	Clinical features of systemic lupus erythematosus
Antiphospholipid antibody syndrome	Positive for antinuclear antibody/anti-double-stranded DNA, low complement C3/C4 levels Patients commonly have large vessel thrombi
Scleroderma renal crisis	May be positive for lupus-type inhibitor, anti-beta-2-glycoprotein, anticardiolipin, antiphosphoserine antibody/antiphosphatidylserine antibody Features of systemic sclerosis Positive scleroderma panel (anti-Scl-70, anticentromere, anti-RNA polymerase III)
Infection	HIV (also <i>Pneumococcus</i> in children)
Posttransplantation (solid organ or bone marrow)	–
Note: ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HELLP = hemolysis, elevated liver enzymes, low platelet count.	

Treatment

Treatment has 3 main principles: reducing antibody levels, increasing ADAMTS-13 levels, and assessing end organs for abnormalities and physiologic support. Importantly, unless there is life-threatening bleeding, platelet transfusions are absolutely contraindicated regardless of the platelet count, as platelets exacerbate the severity of thrombotic microvascular occlusion.³

The mainstay of therapy is daily therapeutic plasma exchanges, with removal of patient plasma and replacement with transfused fresh frozen plasma. This immediately reduces antibody levels and increases ADAMTS-13 levels.³ Where therapeutic plasma exchange is not available, providing plasma infusion — a dosage of 30 mL/kg of fresh frozen plasma is suggested⁶ — can temporarily increase ADAMTS-13 levels while emergent transfer to definitive care is being arranged. If possible, blood samples should be obtained before any plasma is provided; otherwise, establishing the diagnosis may be difficult.

Caplacizumab is an emerging new treatment for TTP that uses an antibody to inhibit the interaction between von Willebrand factor multimers and platelets.⁸ Although therapeutic plasma exchange decreases circulating antibodies, halting the production of antibodies usually requires immunosuppression. Corticosteroid therapy at a dosage of 1 mg/kg per day is a common method of achieving rapid remission.³ Other adjunctive immunosuppressive treatments have been studied, but currently rituximab is the preferred choice for patients at high risk for relapse.⁹

Apart from treatment of the underlying disorder, there is no specific end-organ therapy. End-organ dysfunction can occur in any organ, but most patients present with damage in the brain, kidneys and heart.¹ Neurologic and cardiac manifestations of TTP are associated with the highest mortality rates. Elevated troponin levels are associated with an increased early risk of death.¹⁰ Some patients require hemodialysis.

Patients with TTP are at high risk for venous thromboembolism and should receive prophylaxis with compression stockings and heparin once the platelet count rises above $50 \times 10^9/L$.¹¹

In the era before immunosuppression was used more consistently, relapse rates exceeded 50% and were closely related to ADAMTS-13 function at presentation (< 5% being associated with a high relapse rate) and ADAMTS-13 antibody titres.³ These indices can also be used to follow patients in whom TTP is diagnosed reinstate therapy such as therapeutic plasma exchanges before clinical symptoms develop.

Conclusion

Thrombotic thrombocytopenic purpura is a rare life-threatening hematologic emergency. Because the full pentad of symptoms is present in less than 10% of cases, early diagnosis requires a high index of suspicion. An emergent peripheral smear should be performed in any patient who presents with new or unexplained thrombocytopenia and hemolytic anemia to examine for schistocytes, indicative of microscopic hemolytic anemia. Consultation and transfer of care to an institution with expertise in the treatment of TTP and with plasmapheresis capabilities is necessary. Plasma infusion should be initiated while transfer is being arranged. Patients and families should be informed that this is a life-threatening condition.

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