**Clinical record**

A 27-year-old woman presented with abdominal pain and fever. She was diagnosed with appendicitis and underwent appendicectomy; pathological examination showed acute suppurative and gangrenous appendicitis with no evidence of malignancy or vasculitis. Postoperatively, her haemoglobin level dropped from 161 g/L to 96 g/L, and platelet count from $109 \times 10^9$/L to $38 \times 10^9$/L. Blood film showed schistocytes, helmet cells, spherocytes and thrombocytopenia. Despite transfusion of red cells, fresh frozen plasma and platelets, the blood film appearance continued to deteriorate. She developed tachycardia, hypotension, tachypnoea, oliguria and drowsiness.

A diagnosis of haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) was made based on the blood film and presence of renal impairment, central neurological impairment and fever. Plasmapheresis was started, and she required renal replacement therapy for anuric renal failure. Over the next day, the tachycardia worsened. The following day, she developed respiratory and cardiac failure and decreased level of consciousness, becoming unresponsive to voice. She was intubated and ventilated.

Computed tomography of the brain showed a large region of infarction involving much of the left cerebral hemisphere, particularly the superior portions of the frontal and parietal lobes (Figure 1). A smaller area of ischaemia was also present over the lateral aspect of the right frontal lobe. Troponin T concentration rose from 0.6 to 2.67 μg/L, and an echocardiogram showed impaired left ventricular function with anteroseptal hypokinesis and inferoseptal akinesis. Corresponding changes of inferior ST segment elevation appeared.

The patient required high-dose catecholamine support (noradrenaline, 20 μg/min; dobutamine, 5 μg/kg/min; and vasopressin, 0.2 μg/kg/min) and was considered for an intra-aortic balloon pump. Corticosteroids were started, but her clinical condition remained unstable. She suffered a massive intra-abdominal haemorrhage and developed fixed dilated pupils with a flaccid quadriplegia, her condition deteriorating inexorably to death the following day.

**Discussion**

Thrombotic thrombocytopenic purpura (TTP) was first described in 1924 by Moschowitz, and haemolytic uraemic syndrome (HUS) in 1955 by Gasser et al. Traditionally, the diagnosis of TTP was based on a pentad of symptoms and signs, comprising thrombocytopenia, microangiopathic haemolytic anaemia, renal impairment, neurological symptoms and fever. HUS was considered a paediatric condition, characterised by haemolytic anaemia, renal failure and associated diarrhoea. The two conditions are now believed part of the same disease process, characterised by thrombocytopenia and microangiopathic anaemia. The latter is evidenced by polychromasias, basophilic stippling, nucleated red cells, schistocytes and reticulocytes on the blood film, and a negative direct antiglobulin test. Serum levels of unconjugated bilirubin and lactate dehydrogenase are raised due to red cell destruction, and the latter also indicating diffuse tissue ischaemia. There are degrees of renal abnormality, including raised urea and creatinine levels, proteinuria and haematuria.

HUS and TTP are distinguishable largely by the severity of renal failure and less on the basis of either clinical examination or the traditional tests outlined above. Clinical symptoms include headache, confusion, gastrointestinal symptoms, weakness, fatigue, fever and haemorrhage. Late symptoms are related to microangiopathic thrombosis and, on pathological examination, microthrombi have been found in myocardium, afferent glomerular arterioles, the glomerulus itself, renal parenchyma, adrenocortical arterioles and caecal submucosa with haemorrhagic mucosal ulceration.
Pathogenesis

Although the condition has been known to exist for over 80 years, the pathogenesis is only recently becoming clear. TTP is thought to be caused by hypoactivity of a protease involved in the synthesis of von Willebrand factor (VWF). This factor is synthesised by vascular endothelial cells and megakaryocytes, and is important in platelet aggregation, thrombosis and adhesion.7 The synthesis of VWF involves the cleavage of large VWF multimers by the metalloprotease, ADAMTS-13 (the 13th member of the metalloprotease family A disintegrin and metalloprotease with thrombospondin type 1 repeats).8,9

TTP is believed to result from hypoactivity of ADAMTS-13,10-12 leading to supraphysiological levels of circulating large VWF multimers, which in turn promote platelet aggregation and microthrombosis. This causes a consumptive thrombocytopenia, with haemolysis resulting from trauma to red cells as they pass microthrombi in the microvasculature. ADAMTS-13 activity is undetectable in 90% of TTP cases. Of these, a third are labelled idiopathic (ie, there is no discernible clinical aetiology), while the remainder are associated with clinical conditions that include sepsis and infections, pregnancy, autoimmune diseases and therapy with immunotoxic drugs. The 10% of cases that have detectable ADAMTS-13 activity are associated with disseminated malignancies and organ transplantation. Inactivity of ADAMTS-13 can be hereditary or acquired. The hereditary variant is caused by mutations in the ADAMTS-13 gene (with 75 mutations described by 2005), which are thought to be extremely rare.13 The acquired variant is caused by the protease inhibitor, IgG antiprotease autoantibody.13

In contrast, patients with HUS (whether hereditary or acquired) have normal protease activity. HUS is divided into HUS associated with prodromal diarrhoea (D + HUS) and HUS not associated with prodromal diarrhoea (D - HUS). Verotoxin, named for its cytopathic effect on Vero (African green monkey) cells, is produced by a small percentage of enterotoxigenic Escherichia coli strains. The 0157:H7 strain of E. coli is the primary organism to produce verotoxin, but the toxin is also produced by non-0157:H7 strains. Verotoxin, antibodies to verotoxin and verotoxin-producing E. coli were isolated from patients with HUS, connecting the toxin with the disease.14 The density of verotoxin receptors is 50 times higher on cultured human renal microvascular endothelial cells than on cultured human umbilical vein endothelial cells (VECs). Hence, renal VEC viability and protein synthesis is much more susceptible to the effects of verotoxin than umbilical vein VEC, explaining why renal function is so impaired in patients with D + HUS.15 Free verotoxin is not detected in the plasma of patients with D + HUS, as it is bound to human polymorphonuclear cells; these have a very high affinity for verotoxin, although 100 times weaker than the affinity of renal VECs.

Complement factor H is a human plasma protein that controls the activity of C3 convertases of the alternative pathway of complement activation. Factor H binds C3b, preventing C3 activation — a key step in the alternative

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Figure 1. Computed tomography of the head in a young woman with haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura

Computed tomography revealed a large area of infarction involving much of the left cerebral hemisphere, particularly the superior portions of the frontal and parietal lobes. A smaller area of infarction is also present over the lateral aspect of the right frontal lobe. The ischaemic infarctions are associated with moderate mass effect, with effacement of the overlying cortical sulci and some midline shift.
pathway. Patients with familial D–HUS have been noted to have mutations of the factor H gene, leading to a smaller factor H protein, with only 50% of normal activity. Therefore, lower levels of factor H activity allow higher levels of C3 activation and hence consumption, explaining why a low level of C3 is a factor in HUS/TTP.

The Fas gene encodes a protein important to apoptosis. Plasma from patients with TTP and D–HUS, but not D + HUS, induces expression of the Fas protein and apoptosis in microvascular endothelial cells of dermal, renal and cerebral origins, but not pulmonary, hepatic or large vessel endothelial cells. This indicates a pathological basis for HUS/TTP and gives shape to a new classification of HUS/TTP into TTP and D–HUS in one group and D + HUS in another.

Treatment
Treatment of TTP has improved radically in the past three decades. Massive whole blood transfusion for uncontrolled haemorrhage in a patient with TTP was noted to transiently improve TTP symptoms. This prompted whole blood exchange as a treatment for TTP, but plasmapheresis did not improve TTP symptoms. This prompted whole blood exchange as a treatment for TTP, but plasmapheresis did not improve TTP symptoms. This prompted whole blood exchange as a treatment for TTP, but plasmapheresis did not improve TTP symptoms. This prompted whole blood exchange as a treatment for TTP, but plasmapheresis did not improve TTP symptoms. This prompted whole blood exchange as a treatment for TTP, but plasmapheresis did not improve TTP symptoms.

Corticosteroids are used in conjunction with other therapies, including plasmapheresis, and it is postulated that their effect will be greater in patients with inhibitory autoantibody to ADAMTS-13. Splenectomy is indicated in patients with recurrent relapses and low surgical risk. Vincristine has been used to treat patients whose condition is refractory to plasmapheresis. The mechanism of action and efficacy is unknown.

Our patient’s presentation was typical. She had a recognised aetiology — sepsis — and presented with mild haematological markers of HUS/TTP. Following surgery, she had thrombocytopenia, anaemia with schistocytes, raised serum levels of unconjugated bilirubin and lactate dehydrogenase, pyrexia, renal impairment and neurological symptoms (drowsiness), fulfilling the five traditional requirements for diagnosis. Other causes of vasculitis were excluded on the basis of negative studies for lupus anticoagulant, anticardiolipin IgG and IgM antibodies, extractable nuclear antigen antibody, myeloperoxidase and proteinase-3 antineutrophil cytoplasmic antibody, anti-double stranded DNA antibody and rheumatoid factor. Of interest, she had normal protein C and S and homocysteine levels, marginally low antithrombin III levels, and was negative for β-human chorionic gonadotrophin. Levels of complement components C3 and C4 and haptoglobin were low. She was treated with plasmapheresis and corticosteroids, and, after the second day, the blood film showed some improvement, but her clinical condition deteriorated, leading to macroangiopathic cardiac and cerebral sequelae. Electrocardiogram revealed inferior ST segment elevation, and echocardiogram revealed anteroseptal and inferoseptal akinesis, implying occlusion of the right coronary artery territory. Computed tomography (CT) of the brain revealed a large region of infarction involving much of the left cerebral hemisphere, particularly the superior portions of the frontal and parietal lobes.

In a series of 11 patients with TTP who had CT scans of the brain, seven appeared normal. Magnetic resonance imaging in 12 patients revealed that two had infarctions: one of the posterior and middle cerebral arteries, and the other of the posterior cerebral artery and cerebellum. No series of patients has been described with coronary artery lesions, but one case study describes cardiogenic shock on the background of TTP — coronary angiography demonstrated occlusion of all coronary arteries. A further report of cardiogenic shock on the background of TTP revealed normal coronary arteries with slow flow. There are no descriptions of both cerebral and coronary artery occlusion on the background of HUS/TTP.

Conclusion
The pathophysiology of HUS/TTP is only recently becoming understood. Although primarily a condition of the microvasculature, large vessel thrombosis also occurs. We present a patient who suffered previously undescribed double-organ large-vessel infarction.

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