Investigation vignette

A 70 Year old Man with Aphasia and Agitation

CASE REPORT

A previously healthy 70 year old male awoke with confusion and difficulty speaking. In the Emergency Department he was afebrile and in sinus rhythm, with a heart rate of 76 beats/min. He was agitated, with obvious aphasia. Blood pressure was 150/90 mmHg. He had no neck stiffness. There were no carotid bruits. Examination of cranial nerves and the peripheral nervous system was normal.

Over the next 12 hours his agitation increased. He was moving all limbs with normal power, but did not obey commands and was making incomprehensible sounds. He developed a fever to 38.2ºC, vomited twice, and was passing only 15 - 30 mL/h of dark urine despite fluid loading. CT of his head, carotid Doppler ultrasound and MRI of his head revealed no abnormalities.

Name	Age	Sex
Mr. A. B.	70	M

	Day 1	**Day 2**		
Sodium	142	143	mmol/L	(135 - 145)
Potassium	4.1	4.1	mmol/L	(3.2 - 4.5)
Chloride	105	110	mmol/L	(100 - 110)
Bicarbonate	26	23	mmol/L	(22 - 33)
Creatinine	0.153	0.258	mmol/L	(0.07 - 0.12)
Urea	10.7	19.0	mmol/L	(3.0 - 8.0)
Albumin	41	35	g/L	(33 - 47)
Total protein	77	61	g/L	(62 - 83)
Calcium (alb cor)	2.34	2.16	mmol/L	(2.15 - 2.6)
Glucose	6.5	5.5	mmol/L	(3.6 - 7.7)
LDH	418	861	U/L	(100 - 200)
Bilirubin	37	91	μmol/L	(< 20)
direct bilirubin		17	μmol/L	
AST	27	60	μ/L	(10 - 45)
ALT	14	23	μ/L	(5 - 45)
GGT	28	33	μ/L	(10 - 70)
ALP	72	52	μ/L	(40 - 110)
WCC	12.7	14.2	$x10^9$/L	(4.5 - 11.0)
Hb	148	120	g/L	(130 - 180)
Plt	95	35	$x10^9$/L	(150 - 400)
ESR		10	mm/h	(0 - 42)
INR	0.9	1.2		
APTT	36	45.1	secs	(25 - 42)
Fibrinogen	5.0	4.3	g/L	(1.5 - 4.0)

Figure 1. Plasma biochemical and haematological profiles performed on two venous blood specimens

Diagnosis: Thrombotic thrombocytopenic purpura (TTP).

In support of the diagnosis, the serum haptoglobin measured on Day 2 was < 0.06 g/L (normal range 0.25 - 1.8 g/L), while a blood film revealed fragmented cells, spherocytes and burr cells. The direct antiglobulin test was negative.

Double plasma volume exchanges were commenced. By Day 3 the haemoglobin concentration had fallen to 47 g/L. The patient eventually received 20 exchanges over 3 weeks. He was also treated with prednisone 2 mg/kg daily, although evidence for benefit from steroid therapy is not convincing.[1] To minimise further haemolysis, transfusion was restricted to single unit transfusions if the haemoglobin concentration fell below 70 g/L. For the same reason cryopoor plasma rather than fresh frozen plasma (containing von Willebrand factor) was used as the exchange fluid. Other management included endotracheal intubation, mechanical ventilation, tracheostomy and continuous renal replacement therapy. The patient survived his illness and was eventually discharged home. There was good neurological recovery.

No cause for the TTP was found. Immunoglobulin levels were normal, except IgM which was reduced at 0.43 g/L (normal range 0.5 - 2.0 g/L). Human immunodeficiency and hepatitis A, B and C viral serology were negative. Antinuclear, anticardiolipin and antiphospholipid antibodies were also negative.

The classic TTP pentad consists of microangiopathic haemolytic anaemia, thrombocytopenia, renal failure, encephalopathy and fever. In the related condition of haemolytic uraemic syndrome (HUS), renal failure predominates, whereas in TTP neurological features are usually more prominent. Occasionally both features are florid, as in this case. A combination of thrombocytopenia, schistocytosis on blood film examination and elevated lactate dehydrogenase levels strongly suggests the diagnosis.[2] The source of lactate dehydrogenase is largely ischaemic or necrotic tissue rather than lysed red cells.[3]

The formation of microvascular platelet aggregates is central to the pathogenesis. These contain little or no fibrin, and there is no perivascular inflammation or overt endothelial cell damage. The thrombi are thought to be triggered by abnormally large multimers of von Willebrand factor.[4] Produced by endothelial cells, these multimers are normally cleaved into smaller molecules and released into the circulation by a plasma metalloprotease. Most patients with familial or acquired TTP have very low activity of this enzyme, so that unusually large multimers of von Willebrand factor remain attached to the endothelium. Passing platelets adhere, triggering aggregation and the formation of occlusive thrombi with end-organ ischaemia.[2] Haemolysis is of the microangiopathic type, with telltale fragmentation of red cells.

Although most cases in adults are idiopathic, many associations have been described. These include cytotoxin induced HUS in young children due to bacteria such as Escherichia coli 0157:H7,[5] TTP of pregnancy or the early postpartum period and TTP associated with systemic lupus erythematosis, malignancy, marrow or organ transplantation, total body irradiation, and treatment with drugs such as mitomycin C, ticlopidine, quinine, cyclosporine and tacrolimus. In some of these cases alternative pathogenic mechanisms have been proposed.[1,2]

Although microvascular ischaemia can be widespread, there is a predilection for the renal and cerebral circulations. Neurological disturbances include confusional states, headache, sensorimotor deficits, aphasia, seizures and coma. These are usually reversible provided treatment is prompt. Focal neurological signs are less common. Renal dysfunction ranges in severity from abnormalities of the urinary sediment with mild azotaemia to anuric renal failure requiring dialysis. In one series, approximately 70% of cases presented with a serum urea > 7 mmol/L, and in 17% the initial serum urea was > 20 mmol/L. Over 75% had haematuria, and about the same proportion had proteinuria.[6,7] Ischaemia of retinal, dermal, coronary and mesenteric circulations may also occur. Fever is an inconsistent finding in this syndrome. The presence of high spiking fevers and rigors suggests infection.

Anaemia can be severe. In a Canadian series,[7] the mean haemoglobin concentration on presentation was 89.6 g/L (range 53 - 140 g/L). The haemolysis is non-immune, so that the direct antiglobulin test is negative. Haptoglobin, which binds free haemoglobin, is typically low, and the indirect bilirubin concentration is elevated. Thrombocytopenia is present in most cases, often to less than 20 x 10^9/L. [7] Assays of von Willebrand factor cleaving protease are performed in research centres only.[1] Differential diagnoses include systemic vasculitides, disseminated intravascular coagulation, malignant hypertension, sepsis, disseminated malignancy, and preeclampsia. In contrast to TTP, disseminated intravascular coagulation causes hypofibrinogenemia, with marked prolongation of clotting times. Haemolysis and thrombocytopenia are usually less profound.

TTP has a highly variable presentation making early recognition a challenge. Nevertheless, early recognition and therapy are important to avoid end

organ damage and death. Since the introduction of plasma exchange, the mortality of this condition has fallen from >90% to < 20%.[1]

P. H. SCOTT
Intensive Care Unit, Mater Adult Hospital, South Brisbane, QUEENSLAND

REFERENCES

1. Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Mayo Clin Proc 2001;76:1154-1162.
2. Moake J.L. Thrombotic microangiopathies. N Engl J Med 2002;347:589-600.
3. Cohen JA, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenic purpura. J Clin Apheresis 1998;13:16-19.
4. Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII:von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 1982;307:1432-1435.
5. Karmali MA, Petric M, Lim C, Fleming PC, Arbus GS, Lior H. The association between idiopathic hemolytic uremic syndrome and infection by verotoxin-producing Escherichia coli. J Infect Dis 1985;151:775-782
6. Eknoyan G, Riggs SA. Renal involvement in patients with thrombotic thrombocytopenic purpura. Am J Nephrol 1986;6:117-131.
7. Rock G, Kelton JG, Shumak KH, Buskard NA, Sutton DM, Benny WB. Laboratory abnormalities in thrombotic thrombocytopenic purpura. Canadian Apheresis Group. Br J Haematol 1998;103:1031-1036.