

A case study of thrombotic thrombocytopenic purpura: a 'powerful poison'

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Abstract

This paper presents the case of a previously well 72 year old man who spent 86 days in the intensive care unit (ICU) following a remarkable and explosive presentation of the rare condition thrombotic thrombocytopenic purpura (TTP). TTP is an intravascular platelet aggregation disorder that, without treatment, is associated with significantly high mortality rates. This paper discusses TTP in terms of its presentation, pathophysiology, diagnosis and management. In addition to TTP, the patient developed a number of comorbidities during his stay in ICU. Particular attention is given to two major problems: acute renal failure and prolonged encephalopathy. These issues, along with the initial diagnosis of TTP, resulted in the patient remaining in ICU for a longer period than otherwise might have been expected. Despite many obstacles, the patient recovered and was discharged from hospital 116 days after initial presentation.

INTRODUCTION

A 72 year old man (Mr N) presented to the emergency department of a private hospital in metropolitan Brisbane at approximately 1000 hours after waking during the night with confusion and expressive dysphasia, which initially appeared to improve. Apart from a recent 3 week history of left shoulder pain on abduction, and previous history of excision of melanoma and multiple basal cell carcinomas, mild gastro-oesophageal reflux and appendicectomy, prior medical history was unremarkable. He was a non-smoker, did not take alcohol, used no regular medication, and there were no known drug allergies.

On examination, he was unable to follow simple commands, and could not write his name or short sentences. Expressive dysphasia persisted. The cranial nerves were intact, and there was a good gag reflex. All limbs moved equally, with normal power. Even though he was dysphasic, Glasgow Coma Scale (GCS) score appeared to be 15. Computerised tomography (CT) brain scan was normal. Carotid duplex ultrasound revealed no significant carotid or vertebral artery

disease. 12-lead electrocardiograph (ECG) was normal. Blood pressure was 150/90mmHg. Chest auscultation revealed dual heart sounds and clear air entry. Chest x-ray was normal. The abdomen was soft and he was afebrile. Laboratory findings are presented in Table 1. He was admitted with a provisional diagnosis of transient ischaemic attack (TIA).

In the ward, he developed vomiting, and became less responsive and febrile. He was still quite dysphasic when alerted. GCS at 1600 hours was 15; by 2000 hours this had deteriorated to 11.

There were no other localising neurological signs. Tentative diagnoses now included herpes simplex encephalitis, or middle cerebral artery infarction. Urgent brain magnetic resonance imaging (MRI) was normal. It was thought that he had sepsis and dehydration superimposed on a minor stroke. Urinary tract infection was thought to be the most likely source, but biliary sepsis was also considered. He was treated with intravenous metoclopramide and fluids, and rectal paracetamol. An indwelling urinary catheter (IDC) was inserted, which drained concentrated and possibly bloody urine. Gentamicin was given prior to the collection of urine specimen and blood cultures. Fluid resuscitation was initiated with Albumex 4% and crystalloid. Intravenous ceftriaxone was commenced.

Overnight, he became increasingly agitated, refused oral intake and pulled out his intravenous cannula. Intramuscular haloperidol 5mg was administered with no effect. On examination, he moved all limbs, with normal power. Pupils were equal and reactive to light. He opened his eyes to voice, but did not obey commands, and there was no vocalisation. Urine was dark and scant, with an estimated output of 150ml in 5 hours. There were apnoeic episodes lasting 10-20 seconds. He had received 2.5mg of intravenous midazolam at the time of MRI, so intravenous naloxone 400mcg was trialled but predictably had no effect on apnoeas.

Agitation became progressively worse, and further doses of parenteral haloperidol and midazolam were administered. There was no further urine output, but frank blood was present in the IDC tubing. Blood tests revealed advancing systemic disease. Table 1 illustrates the rapid deterioration in Mr N's condition. He was transferred to the intensive care unit (ICU) at 1230 hours on Day 2, some 24 hours after presentation, and was diagnosed with classic thrombotic thrombocytopenic purpura (TTP).

Table 1. Laboratory findings during the first 48 hours.

	Day 1 1035	Day 2 0835	Day 2 1255	Day 2 1830	Day 3 0615	Day 3 0800	Range*
Haemoglobin	148	120	114	100	47	62	130-180g/L
RCC	4.95	3.96	3.77	3.31	1.53	1.94	4.50-6.50x10 ⁹ /L
Haematocrit	0.428	0.345	0.330	0.287	0.134	0.181	0.40-0.54L/L
Haptoglobin		<0.06					0.25-1.80g/L
C-reactive protein (CRP)		120					<5mg/L
Platelets	95	35	37	34	33	23	150-400x10 ⁹ /L
PT	12.5		15.6	16.2	17.9		11-16 secs
APTT	36.4		45.1	64.1	49.3		25-42 secs
INR normalised ratios (INR)	0.9		1.2	1.2	1.4		2.0-2.5
Serum creatinine	0.153	0.258	0.302	0.334	0.413		0.070-0.120 mmol/L
Blood urea nitrogen (BUN)	10.7	19.0	21.4	23.8	26.8		3.0-8.0mmol/L
LDH	418	861	931	815	260		100-200U/L
Total bilirubin	37	91	93	71	40		<20µmol/L
Total creatine kinase (CK)	99	1707	4096	4066	612		<200U/L
WCC	12.7	14.2	12.5	11.9	8.7		4.5-11.0x10 ⁹ /L
Neutrophils	9.26	11.33	9.77	8.89	7.49		1.8-7.7x10 ⁹ /L

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THROMBOTIC THROMBOCYTOPAENIC PURPURA

TTP was originally described in 1924 by Dr Eli Moschcowitz ¹. It is a rare, classic disease of haematology ², and is the most dangerous intravascular platelet aggregation disorder ³. Moschcowitz suspected a “powerful poison which had both agglutinative and haemolytic properties” ¹ as the cause of this frightening new disease ⁴. TTP is a multi-system disorder, characterised by disseminated platelet aggregation with resultant thrombi formation in the microcirculation, leading to end-organ damage due to thrombotic ischaemia ^{1, 5, 6}. The microvascular ‘hyaline’ thrombi occlude capillaries and arterioles, most commonly in the brain and kidneys (accounting for the dominant clinical features of the disease), but also in the heart, spleen, skin, endocrine glands (adrenals, pituitary), pancreas, eyes, skeletal muscles, ovaries, uterus, testes, gall bladder and lungs ^{3, 4, 7, 8}. Venules are normally not involved ⁹.

Allowing for the expected reaction to necrotic tissue, the inflammatory reaction to the thrombi is remarkably bland ¹⁰. The incomplete vascular occlusions, focal nature of the lesions, and lack of involvement of the venous channels permit sufficient collateral circulation to minimise parenchymatous damage; hence the potential for reversibility of the dysfunction of involved organs ¹⁰. Historically, TTP has been associated with a mortality rate of at least 90% ¹¹. Even as late as 1965, most patients diagnosed with TTP died ¹². With therapeutic plasma exchange, TTP has become a curable illness ², although it remains enigmatic from the perspective of its aetiology, pathophysiology and treatment ¹³.

Clinical manifestations/diagnosis

The presentation of TTP may be variable 8. A prodromal phase resembling a virus-like disease has been described in up to 40% of patients 14. Other presenting symptoms include weakness, malaise, fatigue, nausea and vomiting, pallor, jaundice and scleral icterus 5, 6, 12, 14-16. Occasionally, the chief complaint may include the onset of pain at different locations such as joints and muscles (arthralgia and myalgia 7). Mr N complained of shoulder pain of three weeks' duration prior to presentation. Muscular ache is caused by skeletal muscle ischaemia and myolysis 17.

In over 90% of patients, purpura may be the initial manifestation 15, and is a consequence of the severe thrombocytopaenia 5. TTP is primarily a disorder of microcirculatory thrombosis, and severe or significant haemorrhage is rare 16, 18. However, purpura may be associated with gross haematuria 15, which has been a clinical feature in several studies 10, 14. Other manifestations include epistaxis, gingival haemorrhage, gastrointestinal bleeding (including melaena and haematemesis), menorrhagia, haemoptysis, and retinal, choroidal or vitreous haemorrhages 5, 7, 14. Petechial haemorrhages in the skin and ecchymoses are the most frequent forms of bleeding manifestations 7, 14. Generalised bruising/purpura was noted when Mr N was admitted to ICU. Patients can also suffer from visual defects because of microvascular ischaemia in the retinal circulation 16. Severe abdominal pain as a major presenting symptom is prominent in many series 12, 14. Abdominal pain presumably reflects bowel ischaemia due to microvascular obstruction 19. Abdominal pain may also be caused by TTP-associated pancreatitis 20.

In classic cases, patients present with a pentad of clinical and laboratory findings:

- Microangiopathic haemolytic anaemia (MAHA);
- Thrombocytopaenia;
- Neurologic symptoms and signs;
- Renal function abnormalities; and
- Fever 14.

MAHA and thrombocytopaenia are the laboratory hallmarks 21. The anaemia that develops in TTP is a haemolytic type that is mechanical in origin 16. As red cells traverse high shear areas of microcirculation that are partially occluded by aggregating platelets, erythrocyte fragments are produced 4. This striking morphological feature of the peripheral blood (i.e. fragmentation) provides the most help in making the diagnosis of TTP 16.

Detection of fragmented red blood cells (schistocytes) with the typical aspect of burr or helmet cells – together with a negative Coombs' test (thus excluding immunologic destruction of

erythrocytes) – are needed to confirm the microangiopathic nature of the haemolysis 4, 7, 11, 21.

Thrombocytopenia is usually severe, with platelet counts below $20 \times 10^9/L$ in most cases 3, 16. The degree of thrombocytopenia reflects the extent of intravascular platelet clumping 4. Intravascular platelet aggregation also results in reduced platelet survival time 5. Thrombocytopenia may be the earliest laboratory finding, preceding the full-blown syndrome 17. Mr N was thrombocytopenic at presentation; other haematological values were still essentially normal at that time.

TTP in its classic presentation is that of an acute change in mental status or neurologic function 22. Headache, altered state of consciousness, including somnolence, confusion and stupor, behavioural changes, syncope, vertigo, ataxia, visual symptoms, cranial nerve palsies, stroke, aphasia, dysarthria, slurred speech, paraesthesia, paresis, and focal or generalised seizures may be the presenting manifestation, or develop in the course of the disease 15, 17. Alteration in the state of consciousness may progress abruptly to coma 17. The initial neurologic manifestations are often transient and fluctuating; this rapid ‘waxing and waning’ of neurologic symptoms may be diagnostic for TTP 14.

These bizarre symptoms are in keeping with transient occlusion of the cerebral microcirculation by platelet aggregates 17. There is an ‘opening up’ of collateral circulation, and the persistence of some patent vessels to a given area of brain 23. Mr N’s presentation was consistent with this pattern, in that his dysphasia initially appeared to improve. Despite widespread vascular occlusions in the brain and severe neurologic manifestations, extensive infarction is unusual, and CT brain scan is often normal 7, 14, 17. Fever, if present, is usually low-grade 6, and is presumably due to hypothalamic ischaemia and/or tissue necrosis 17.

It is to be expected that the kidney, as the most vascular organ in the body, should be involved in a disease process in which the major pathologic feature was recognised from the outset as widespread microvascular thrombi 10. The presence of some degree of renal involvement as an essential component in most cases of TTP is well-established 14. Renal abnormalities are present in 50-90% of episodes 10, 24, 25. However, renal insufficiency is usually mild 15.

Abnormalities such as microscopic haematuria, and proteinuria with casts, are an almost constant feature 10, 15, 17. Oliguria and acute renal failure are uncommon 12, and dialysis is usually not required 26. Early diagnosis is important for two reasons:

- Mortality in untreated patients may be as high as 80-90% 2, 3 It is possible that the true mortality is underestimated as the majority of deaths occur within 48 hours after presentation 11.

- TTP has an excellent prognosis after adequate treatment 27.

Before the era of effective treatment, TTP was diagnosed by the defining classic pentad of symptoms and physical findings 14. Diagnosis is frequently difficult, however, because the pentad is often incomplete at initial presentation 2, 3, 11. The danger is that by the time all five criteria are fulfilled, severe end-organ ischaemia has developed 16. Therefore, to avoid a potentially harmful delay in treatment, the diagnosis of TTP is frequently invoked when thrombocytopenia and MAHA alone are present, in the absence of another likely cause 13. However, some patients may not be anaemic at the outset 2, although anaemia may progress rapidly following diagnosis and treatment 28 (Table 1). Similarly, red cell fragmentation may not appear until a day or two following clinical presentation 4.

In Mr N's case, spherocytes, fragmented cells and burr cells did not appear until Day 2, more than 24 hours after admission.

Thrombocytopenia and MAHA are obviously non-specific criteria 29 and, as a result, the diagnostic margins of this syndrome are inevitably indistinct 28. Thrombocytopenia and haemolysis, as well as renal failure, are all common abnormalities in critically ill patients and often the aetiology is not clear. Therefore, TTP must be considered 28. Table 2 is a summary of important conditions that may mimic TTP.

Other diagnostic considerations

Haptoglobin is a glycoprotein that is synthesised in the liver. When red cells are destroyed in the vascular compartment, the haemoglobin escaping into plasma is bound to haptoglobin 30. In haemolytic anaemias characterised by intravascular haemolysis, catabolism of haptoglobin is so rapid that it basically disappears from the plasma³¹. Mr N's haptoglobin on Day 2 was $<0.06\text{g/L}$ (range $0.25\text{-}1.80\text{g/L}$). Evidence of intense haemolysis is also indicated by reticulocytosis (an index of accelerated erythropoiesis 32), which is increased to a degree appropriate for the severity of the anaemia 33. Reticulocyte count on Day 2 was normal, but polychromasia (a sign of red cell immaturity 34) was noted on Day 4. Leukocytosis is often present but is generally less than $20,000\text{ cells/mm}^3$ 15.

Because haemolysis is of the intravascular type, haemoglobinuria is usually present 33. Free haemoglobin was present in Mr N's urine on Day 3. Hyperbilirubinaemia (mainly unconjugated) is an additional specific indicator of the accelerated red cell disruption 21. Serum lactate dehydrogenase (LDH) is almost invariably increased 17 due to the release of red blood cell LDH as a consequence of intravascular haemolysis, as well as systemic microvascular compromise³⁵. Cohen et al. 35 found that 90% of patients manifested significant elevation in isoenzyme LDH5, which is derived from

skeletal muscle and liver. Mr N's total creatine kinase (CK) on presentation was 99U/L (range <200U/L). By Day 2 this had risen dramatically to 4098 U/L.

Despite widespread platelet agglutination, TTP is not a primary disorder of coagulation or thrombin activation, so coagulation studies such as the activated partial thromboplastin time (APTT) and prothrombin time (PT) are characteristically normal 16 or only mildly disturbed 7, which helps to differentiate this condition from disseminated intravascular coagulation (DIC) 9. Fibrinogen levels are usually normal 9, 16. Mildly elevated fibrinogen degradation products (FDPs) have been reported 7. Table 3 summarises the characteristic laboratory abnormalities of TTP.

Aetiology

Precise figures relating to the incidence of TTP are elusive. The incidence in the United States may vary from one case per million people to one in 6,000 12, 36. The incidence in Australia is unclear, but only 13 different adults have been treated at the Mater Hospital apheresis unit in the past 5 years 37. TTP usually occurs in previously healthy people 33, and may occur in all age groups 14. It is more frequent in women, with a female to male ratio of 3:2 12, 14. Many clinical events regarded as possible precipitating factors for the disease have been reported. Multiple drugs have been causally implicated, including mitomycin, cyclosporine, tacrolimus and quinine 16, ticlodipine 38 and alcohol 39. There have been reported associations with countless bacterial and viral infections 40, including human immunodeficiency virus (HIV) 41; connective tissue diseases such as systemic lupus erythematosus (SLE) 16; as well as pregnancy, malignancy, bone marrow transplantation and total body irradiation 16. Genetic and environmental influences 42, 43 have also been proposed. Other more obscure associations include bee sting 44, dog bite 45 and carbon monoxide poisoning 46. However, the majority of cases are truly idiopathic 6, and most patients have a single acute episode that never recurs after successful therapy 5.

Pathophysiology

The hypotheses concerning the pathophysiology of TTP are controversial, and suggest different pathogenetic mechanisms being responsible for development of the disorder 5. Several lines of evidence suggest that von Willebrand factor (vWF) is involved 26:

- TTP thrombi contain, in addition to platelets, an abundance of vWF, but little or no fibrinogen/fibrin 47.
- vWF is present on the surface of platelets in patients with TTP 4.
- Unusually large vWF multimers (ULvWF) are present in TTP plasma 48.

The entire constellation of vWF multimers found in the normal circulation is produced within both megakaryocytes and endothelial

cells, and is stored within the α -granules of platelets and the Weibel-Palade bodies of endothelial cells 4. Megakaryocytes and endothelial cells also construct ULvWF, which are not a normal constituent of circulating plasma 4. The presence of ULvWF in TTP plasma may reflect the failure of the plasma to process adequately the ULvWF released from endothelial cells 4.

It has been found that TTP is associated with a severe deficiency of a vWF-cleaving metalloproteinase 49. In the absence of this proteinase, vWF is not cleaved to smaller forms 50. The uncleaved, ULvWF may be more effective at binding under the influence of elevated fluid shear stresses (such as that encountered in arterioles and capillaries 39) to platelet receptors and complexes, resulting in metalloproteinase activity has been detected in many of the patients studied in detail 50.

Interestingly, it has been found that some individuals with congenital proteinase deficiency have never had an acute TTP event 39. This indicates that a deficiency of vWF-cleaving proteinase alone may not be sufficient to cause acute TTP 39. Many authorities believe that microvascular endothelial dysfunction or injury is an important step in the sequence of events leading to disease manifestation 5, 39. Some kind of trigger (drugs, bacteria, pregnancy etc.) leads to activation or death of the microvascular endothelial cells 39. Endothelial damage is known to result in the release of high molecular weight forms of vWF from the Weibel-Palade bodies and their appearance in the regional circulation 51.

The majority of patients have a quantitative elevation of vWF 24, which supports the generally accepted concept that TTP is ultimately related to some form of endothelial cell damage or stimulation 52. In Mr N's case, vWF:Ag levels were raised on Day 2, at 1.79U/ml (range 0.5-1.6U/ml).

Table 2. Differential diagnosis of TTP.

• Haemolytic uraemic syndrome ⁹
• DIC ⁹
• Evans syndrome ^{*4}
• Malignant hypertension ⁴
• Sepsis (bacterial, viral, fungal, rickettsial) ¹⁸
• Malfunctioning prosthetic cardiac valve ⁴
• Disseminated malignancy ¹⁶
• Pregnancy <ul style="list-style-type: none"> – Pre-eclampsia/eclampsia⁴ – HELLP syndrome^{†4}
• Systemic vasculitis (SLE, scleroderma) ¹⁸
• Heparin-induced thrombocytopenia/thrombosis ²

* Concurrent autoimmune thrombocytopenia and direct Coombs' test-positive autoimmune haemolysis⁴
 † Haemolytic anaemia, elevated liver enzymes, and low platelets⁴

Table 3. Characteristic laboratory abnormalities of TTP 16.

MAHA
• Fragmented red blood cells (schistocytes) on peripheral blood smear
• Reticulocytosis
• Increased indirect bilirubin level
• Decreased haptoglobin
• Negative direct Coombs' test
Thrombocytopenia
• Platelet count often lower than $20 \times 10^9/L$
Coagulation studies
• Normal APTT and PT
• Negative DIC screen
Markedly increased LDH level (tissue ischaemia and haemolysis)
Variably increased creatinine and BUN

Management

In view of Mr N's extreme agitation on arrival in ICU, he was intubated and mechanically ventilated in order to facilitate insertion of a subclavian central venous line, radial arterial line and femoral vascath, in anticipation of commencing plasma exchange. The femoral site is generally the first choice, as haemostasis may be

assisted by local compression as needed 18. All puncture sites immediately began to ooze. There was also fresh blood oozing around the IDC, with blood and clots draining from within the IDC, requiring continuous bladder irrigation. Frusemide infusion was commenced at 30mg/hour, in view of deteriorating renal function. Plasma exchange was commenced at approximately 1900 hours on Day 2.

There is probably no other disease in which prompt diagnosis and treatment can lead to as great a difference in clinical outcome as with adult TTP¹⁸. The accepted standard of care for TTP, and indeed, the critical element of treatment, is daily plasma exchange^{2, 13}, i.e. the combination of plasmapheresis and plasma infusion with normal platelet-poor fresh frozen plasma (FFP)⁴. Acute TTP can be treated successfully by intensive plasma manipulation in nearly 90% of patients^{24, 25}. A delay in initiating plasma exchange may result in treatment failure¹⁸.

Plasma exchange requires a large-diameter, dual-lumen central venous catheter, similar to that required for haemodialysis (HD). The patient's blood is withdrawn, and the plasma is mechanically separated from cells by centrifugation. The patient's cells are then returned with fresh, therapeutic donor plasma⁵³. It is presumed that harmful substances such as ULvWF and autoantibodies against vWF-cleaving metalloproteinase are removed by plasmapheresis⁴, and that the infusion of normal plasma provides supplemental quantities of the vWF-cleaving metalloproteinase that is inhibited by autoantibodies^{49, 50}. Studies on serial plasma samples show that plasma proteinase activity rises after patients are treated with plasma therapy⁵⁰.

Usually, one plasma volume equivalent to 40ml/kg of body weight is exchanged per session²¹. Mr N's regime involved volume exchanges of 1.0, 1.5 and 2.0 plasma volumes; the majority were double plasma volume exchanges. There are no clinical data to support a frequency of plasma exchange exceeding once per day¹¹, nor do there appear to be any scientific studies that have precisely determined the optimal treatment schedule. Some patients recover after one plasma exchange²⁸, while others require prolonged therapy⁹. In one case, 145 exchanges over 221 days were required²⁸. The median number of treatments is about 15 over 3 weeks²⁸. Mr N required 21 exchanges over a period of 31 days to achieve a remission (one session was aborted after an hour because of a massive upper gastrointestinal bleed).

If a delay in institution of plasma exchange is unavoidable for technical reasons, or if it is unavailable, as in a distant rural site, it is appropriate to initiate therapy with plasma infusion and glucocorticoids²⁹. However, plasma infusion should not be viewed as an acceptable alternative to plasma exchange for anything but a

short-term measure 18. A randomised controlled trial comparing plasma infusion with plasma exchange definitively confirmed the superiority of the latter 24. The infusion of FFP alone may be associated with an increased rate of relapse 25, as well as the risk of volume overload, which is increased by renal insufficiency 4. Until relatively recently, established practice was to use FFP as the replacement fluid in plasma exchange 54. To optimise the management of TTP, alternatives to FFP have been sought 11.

Cryoprecipitate-poor plasma (CPP), or cryosupernatant, is one such option 11. CPP is the residual plasma fraction after the separation of cryoprecipitate, and is mostly depleted of vWF, fibrinogen, fibronectin and factor XIII 18, 21. CPP is a logical option because it lacks ULvWF multimers, which have been implicated in the pathophysiology of TTP 11, while at the same time retaining vWF-cleaving proteinase activity 4. The superiority of CPP over FFP in terms of improved response rates and lower mortality has been demonstrated 54. The replacement fluid used for Mr N's plasma exchange consisted of 100% CPP, or CPP in combination with FFP. 4% albumin was introduced as a partial exchange fluid at the ninth exchange on Day 10 because of a persistent metabolic alkalosis. Plasmapheresis commonly induces metabolic alkalosis in TTP patients, probably due to the high citrate content of FFP 55. Encouraging findings have been reported with a combination of 5% albumin and plasma (CPP/FFP), in terms of response time and mortality rate 13, but the potential benefits of albumin as partial replacement require further study 13.

Response to plasma exchange/ therapeutic targets

The response to plasma exchange may be variable, perhaps reflecting the heterogeneity of TTP syndromes 2. An initial response may occur within minutes of beginning the first exchange, or may not be observed for over 1 month 25. Thrombocytopenia typically requires several days for initial recovery to begin 2, 53. Large day-to-day fluctuations in the platelet count are common, particularly when plasma therapy is instituted 7. Mr N's platelet count dropped to $23 \times 10^9/L$ on Day 3, remained below 50 until Day 6, and did not exceed 100 until Day 10. Platelet count did not normalise (160) until Day 28.

A recent survey of 20 institutions in the United States confirmed the wide variability of therapeutic targets 13. However, serum LDH and platelet count generally appear to be the most important parameters on which treatment decisions are based 2, 21. A platelet count of at least $150 \times 10^9/L$ appears to be a requirement for discontinuation of daily plasma exchange 13, but others accept platelet counts of 100 or 200 13. However, on completion of the first cycle of plasma exchange on Day 17, Mr N's platelet count was just $38 \times 10^9/L$. Whereas treatment decisions based on platelet count

appear to be widely popular, measurement of serum haptoglobin is rarely mentioned in discussions of therapeutic targets. In Mr N's case, haptoglobin level was regarded as an important indicator of clinical improvement or deterioration. Mr N commenced plasma exchange on Day 2, when haptoglobin was <0.06 g/L (range 0.25-1.80 g/L). On Day 17, haptoglobin was normal at 1.4g/L. On this basis, rather than the platelet count, plasma exchange was discontinued.

Many patients have a prompt exacerbation of thrombocytopenia and haemolysis when plasma exchange is tapered. In these patients, it is assumed that TTP has remained active and requires continued treatment for control 28. Mr N's first treatment cycle consisted of 16 consecutive daily treatments. At approximately 29 hours after completion of the first cycle, red cell count (RCC) had dropped from 3.17 to $2.63 \times 10^{12}/L$, and haemoglobin from 91 to 77g/L. By Day 23, haptoglobin had dropped to 0.3g/L, although platelets had improved somewhat to $61 \times 10^9/L$. He received further plasma exchange on Days 24 and 25. By Day 29, haptoglobin had again dropped to <0.06 g/L. Platelets had improved to $192 \times 10^9/L$ but RCC was still only $2.77 \times 10^{12}/L$, and haemoglobin 78g/L.

Additional plasma exchange was performed on Days 29, 31 and, finally, on Day 32. At that time, platelets were $313 \times 10^9/L$, haemoglobin 100g/L, RCC $3.41 \times 10^{12}/L$ and haptoglobin (on Day 30) 0.2g/L. On Day 35, three days after the last plasma exchange, haptoglobin was normal at 1.3g/L, and remained so thereafter. As with platelets, similar variability has been seen with LDH therapeutic targets 13. Some institutions require LDH to be within their normal reference ranges prior to discontinuing daily plasma exchange, while others discontinue treatment as long as LDH is approaching the patient's baseline (near normal). Some centres do not follow LDH in their management of TTP 13. LDH may improve promptly 2 and become normal before recovery of the platelet count, or may remain slightly elevated for several weeks 28. Mr N's LDH normalised on Day 15, but had risen again by Day 22. On the final day of plasma exchange (Day 32), LDH remained high at 415 U/L, and essentially remained elevated until Day 100. However, there were many contributory factors in this setting.

Schistocytes in declining numbers often persist for many days on peripheral blood films, and so cannot be used as a reliable marker of remission 4. Occasional fragmented red cells were still present on film on Day 87. Anaemia may continue to worsen and further red cell transfusion is often required 2, based on the critical haemoglobin level and degree of haemolysis 16, and also if the patient has symptoms of shock or insufficient tissue oxygenation 22. Mr N received many transfusions of packed cells (at least 78 units), but normal values for both RCC and haemoglobin were never achieved during his hospitalisation.

Ancillary therapies

In the past, the widespread platelet aggregation observed in TTP has led to the use of platelet inhibitor drugs (PID), including aspirin, dipyridamole, sulfinpyrazone and dextran 8. PID have been associated with haemorrhagic complications in severely thrombocytopenic patients 24, 25. Therefore, they cannot currently be recommended for patients with TTP who have profound thrombocytopenia 16. On the other hand, given the proposed autoimmune pathogenesis (i.e. the demonstration of autoantibodies abolishing vWF-cleaving proteinase activity in many cases 4), a strong rationale for steroid use now exists 49, 50.

Glucocorticoids may suppress the production of autoantibodies against the vWF-cleaving metalloproteinase 3. Because of the efficacy of plasma exchange, assessing the additional benefit of ancillary therapies such as glucocorticoids has been difficult 16. However, it is prudent to institute glucocorticoid therapy – in association with plasma exchange – in all adult patients with initial TTP episodes, unless there is a strong contraindication 4. The recommended dosage is 200mg/day of intravenous prednisolone 3. Mr N was commenced on methylprednisolone on Day 2, at a dose of 100mg twice daily. The dose was reduced to 100mg daily on Day 13 and ceased on Day 14.

Platelet transfusion

Patients with TTP have experienced abrupt, striking deterioration after platelet transfusion 25. Generally, platelets should not be transfused because they are thought to increase clumping and worsen the associated microvascular disease 56. There have been reports of fatalities 56. If the platelet count is very low and bleeding is severe or life-threatening (such as intracranial bleeding) 4, 21, 27, transfusion of platelets at a slow rate (to minimise the risk of microvascular occlusion 3) will be necessary 4. Platelet infusion may also be required before invasive procedures 21. Packed red blood cells, on the other hand, are depleted of platelets and can be given safely 18.

Mr N received several units of platelets following a massive upper gastrointestinal haemorrhage, and prior to percutaneous tracheostomy (this procedure was abandoned following major haemorrhage into the trachea on wire insertion). Further platelets were given prior to surgical tracheostomy. Administration of platelets in these instances did not appear to intensify the disease process.

Encephalopathy

Although neurological symptoms usually dominate the clinical

picture in TTP 21, and may worsen in the initial days after diagnosis 24, they are often reversible with expeditious treatment 16. Non-focal neurologic symptoms, such as mental status changes, may resolve immediately and dramatically 2, 53, or may subside within 48 hours after initiation of plasma therapy 2. The observation that many comatose patients with TTP become alert during plasmapheresis and plasma exchange establishes that this is effective therapy 25. TTP patients have also recovered from prolonged comas without neurological sequelae after receiving intensive plasma exchange 57. Therefore, even if a patient is comatose and does not respond to initial treatment, repeated plasma exchange and other supportive therapies should be maintained 9.

Mr N's neurological status became an issue of serious concern during his stay in ICU. He became encephalopathic during the early days of his illness, and this persisted for a significant period of time. The prolonged encephalopathy was variably attributed to TTP with small cerebral vessel disease (even though encephalopathy persisted long after TTP was deemed quiescent), steroids, critical illness, cytokines, and metabolic and drug factors. He became extremely agitated whenever sedation was lightened, with head thrashing and continuous non-specific limb activity. Nursing him was very difficult, in terms of maintaining integrity of the endotracheal tube/tracheostomy, ventilator/humidifier circuit, and invasive lines. It was also distressing for Mr N's family to see him in this condition. A number of sedation regimes were implemented, including various combinations of fentanyl, midazolam, propofol, methadone, haloperidol and diazepam.

Sedation was complicated by marked hypotension, even with small boluses of sedatives. Noradrenaline was required for a period. CT brain scans on Days 11 and 36 were normal. Encephalopathy was a persistent feature. Mr N did not obey commands until Day 51, at which time he was sedated solely with propofol. Neurological status improved (albeit extremely slowly) from this point, with boluses of midazolam and propofol as required to allow trouble-free operation of dialysis equipment.

Renal failure

Haemoglobinuria and hyperbilirubinaemia may have nephrotoxic effects in the presence of extracellular volume depletion 10. Given the critical state in which some of these patients present, a compromise in the extracellular fluid volume is a common problem. Fluid replacement should be an early and integral part of the supportive therapy of every patient with TTP 10.

While plasma exchange obviously has a dramatic effect on the course of TTP, the renal prognosis of patients so treated remains unclear 58. Plasma exchange typically reduces the need for HD 18,

but a minority of patients require urgent HD 8, and its use to achieve rapid volume control and correction of uraemia occupies an important role in the management of such patients 10. A higher serum creatinine at presentation may be associated with the eventual need for HD 58. Continuous renal replacement therapy (CRRT), using a PRISMA

CFM TM machine, was commenced on Day 5 for a creatinine of 0.551mmol/L and urea of 38.0mmol/L. Urine output was frusemide-driven. There was also an element of fluid overload, with a conservatively estimated positive fluid balance of 3.6L. In order to limit the number of vascular access devices, with their attendant risks (in particular, the potential for bleeding complications), it was preferable to use the same device for both plasma exchange and CRRT. The logistics of this were often complicated, but nursing staff quickly settled into a routine whereby Mr N was dialysed immediately following completion of daily plasma exchange. Continuous veno-venous haemodiafiltration (CVVHDF) was the mode of choice. Gambro haemofiltration solution (formula no. 1) was used.

Mr N received approximately 704 hours of CRRT over a period of 45 days. Blood flow of 120-180ml/minute was used, according to his haemodynamic status. He was generally able to tolerate a blood flow of 180ml/minute. Filtration and dialysate rates of 1000-2000ml/hour were used. Fluid was removed at a rate of 0-500ml/hour, according to fluid balance and haemodynamic parameters. CRRT was discontinued on several occasions to observe the effect on renal parameters, but renal function remained dialysis-dependent until CRRT was finally ceased on Day 58. Renal failure in TTP patients may worsen before improvement is noted 2, and it often resolves more slowly than other parameters 18.

Table 4. Summary of Mr N's co-morbidities during 86 days in ICU.

• Prolonged wean from mechanical ventilation
• Bilateral pleural effusions requiring drainage
• Pericardial effusion
• Marked cardiovascular lability (hyper/hypotension)
• Atrial fibrillation
• Gastroparesis/ileus; poor absorption of enteral nutrition; sluggish bowel function; profuse diarrhoea
• Passive regurgitation of gastric contents leading to contamination of tracheostomy site
• Para-urethral trauma (? false passage) with frank haematuria
• Bladder atony
• Massive upper gastro-intestinal haemorrhage with recurrent episodes of lesser severity (diffuse erosive gastritis and reflux oesophagitis)
• Likely ischaemic colitis/enteritis secondary to TTP
• Recurrent melaena
• Abdominal ascites
• Muscle loss and debilitation
• Infective complications: <ul style="list-style-type: none"> – nosocomial lower respiratory tract infection; – sepsis of uncertain origin; – oral herpes simplex; – flank cellulitis; – groin candida and intertrigo/maceration of areas of the neck (thus limiting vascular access sites); – low grade tracheostomy infection/cellulitis; – gram-negative and candidal urinary tract infections; – klebsiella bacteraemia

Many patients who develop renal failure requiring dialysis subsequently recover renal function 58, although it may take several months, and may be incomplete in many cases 53. However, a persistent azotaemia does not necessarily indicate failure of therapy 18, and the development of chronic renal failure is uncommon 14, 15. A mild renal impairment persisted until Mr N was discharged from hospital.

Mr N was ready for transfer to the ward on Day 72. He remained mildly confused. Other issues that emerged during his stay in ICU are summarised in Table 4. Unfortunately, he was readmitted to ICU on Day 78 with nausea, vomiting, abdominal pain and a rising white cell count (WCC). Laparotomy revealed gross peritonitis, a possibly perforated jejunal diverticulum and gangrenous acalculous cholecystitis. Small bowel resection and cholecystectomy were performed. There followed another period of mechanical ventilation. Wound closure was delayed until Day 81, and he was extubated on Day 85. Mini-tracheostomy was required for sputum clearance. Multiresistant *Acinetobacter calcoaceticus* was identified

in intra-abdominal and peri-tracheal specimens, as well as in sputum. Mr N was transferred to the ward on Day 92, and was discharged from hospital on Day 116.

CONCLUSION

TTP is a rare, potentially life-threatening disease of haematology. Patients may present with a diverse array of symptoms; however, renal and neurologic manifestations are prevalent. MAHA and thrombocytopenia are essential diagnostic considerations. The aetiology and pathophysiologic mechanisms of TTP remain uncertain and debated. vWF is likely to be involved, as is a deficiency of a vWF-cleaving metalloproteinase.

The accepted standard of care for TTP is daily therapeutic plasma exchange. CPP is the preferred replacement fluid. Additional therapies include administration of glucocorticoids. Red cell transfusion is often required, but platelet transfusion has been associated with adverse outcomes. Therapeutic targets may vary between institutions. Critically ill patients such as Mr N require intensive supportive care, not only in terms of managing TTP, but also from the perspective of treating coexisting illnesses or the complications that inevitably arise during a prolonged stay in ICU (TTP patients with severe renal and neurologic impairment often have a more protracted clinical course before remission is achieved 59). TTP is a frightening, complicated and perplexing disease. Early diagnosis and treatment are absolutely essential if a positive outcome is to be achieved.

Postscript

This was a most severe case of TTP, and medical and nursing staff were often dismayed by Mr N's apparent lack of progress. At times the outlook appeared bleak, with limited new treatment options, other than time and patience. Mr N's wife and family visited daily, and the strain associated with this, especially for his slightly frail wife, was obvious. However, there is no doubt that the unwavering support provided by Mr N's family played a significant role in his recovery. Mr N and his wife visited the ICU 3 weeks after his discharge from hospital. There was no sign of TTP, and only very modest renal impairment. He had regained full independence with mobility and other activities of daily living, and was generally making an outstanding recovery from the multitude of problems that plagued him during his stay in ICU

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