A diagnosis not to miss

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INTRODUCTION

The clinical presentation of this disease overlaps with other more common illnesses. This article presents a case which was initially mistaken for sepsis. Early diagnosis is essential because specific therapy is required as soon as possible to prevent death.

CASE REPORT

A 45-year-old woman attended accident and emergency after fainting and feeling unwell with a fever. Blood and protein were noted in the urine. A diagnosis of urinary tract infection was made and she was sent home with antibiotics. She became increasingly unwell with fever, headache and confusion before collapsing the following day.

On examination her Glasgow Coma Score was 7/15, with a fever of 38.2°C, respiratory rate of 35/minute, pulse of 120/minute and blood pressure of 160/95 mmHg. She had a widespread petechial rash. Tone was increased in all four limbs and she had extensor plantar responses. There was no neck stiffness. Her pupils were equal and reactive, but her gaze deviated to the right. Soon afterwards she had a focal fit involving the left side of her body. Her blood results were: sodium 142 mmol/litre, potassium 2.8 mmol/litre, urea 9.1 mmol/litre (blood urea nitrogen 25.3 mg/dl), creatinine 120 mmol/litre (1.44 mg/dl), glucose 12.5 mmol/litre (208 mg/dl), haemoglobin 7.7 g/dl, total white cells 21.8 x 10^9/litre (neutrophils 14.2 x 10^9/litre), platelets 8 x 10^9/litre. Arterial blood gases and coagulation studies were normal. A contrast computed tomography scan of the brain, performed under general anaesthesia, was normal.

1. What would your management of this case be in the first hour?
2. What are the possible diagnoses?
3. What would your subsequent management be?

The diagnosis was initially thought to be sepsis and the haematology team was contacted to request a platelet transfusion. However, given the clinical history, the blood picture and normal coagulation studies, a diagnosis of thrombotic thrombocytopenic purpura was suggested. The blood film is shown in *Figure 1*. Emergency plasmapheresis was commenced on the intensive care unit daily for 10 days until her haematological parameters were normal. She continued to have plasma infusions as an outpatient two to three times a week for 2 months and eventually made a full recovery.

COMMENTARY

Thrombotic thrombocytopenic purpura (TTP) is one of the thrombotic microangiopathic haemolytic anaemias (MAHA). These are microvascular occlusive disorders characterized by platelet thrombi in small blood vessels, resulting in a consumptive thrombocytopenia and intravascular haemolysis caused by mechanical damage to circulating erythrocytes (Moake, 2002). Although all organs may be involved, TTP classically affects the brain, kidneys, pancreas, spleen and adrenal glands, with potentially fatal consequences (Nabhan and Kwaan, 2003).

In the past, a diagnosis of TTP required a pentad of thrombocytopenia, MAHA, neurological abnormalities, fever and renal dysfunction. This has been superseded by a diagnostic dyad of thrombocytopenia and MAHA which is direct antiglobulin test (DAT) negative, with no other obvious cause – as the remaining signs are often absent in early disease (Rock, 2000). In contrast to disseminated intravascular coagulation, coagulation studies are usually normal in TTP (Rock et al, 1998) and this was a clue to the diagnosis in this case. The clinical picture may be complicated by the presence of non-specific influenza-like symptoms, muscular, joint or abdominal pains. Neurological signs can be bizarre. Renal involvement is usually mild, otherwise haemolytic–uraemic syndrome must be considered, which is a closely related disease and is managed differently (Moake, 2002).

The vast majority of TTP is acquired. In approximately 40% of patients it is idiopathic, although there are many recognized associations (*Table 1*). Up to 25% of TTP may occur in pregnancy or post-partum (Proia et al, 2002) and TTP must be distinguished from pre-eclampsia, eclampsia and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (McMinn and George, 2001).

In TTP there are unusually large multimers of von Willebrand factor (vWF) present in the plasma. These vWF multimers bind platelets, causing increased platelet aggregation and attachment to the subendothelium (Nahban and Kwaan, 2003). Normally these vWF multimers are cleaved by a specific protease which is deficient or inhibited in TTP. There are no readily available tests for vWF-cleaving protease activity.

Management in the first hour should focus on management of A (airway), B (breathing), C (circulation) and D (disability) in any patient who is critically ill. Urgent haematol-

Figure 1. Blood film showing thrombocytopenia and the typical features of microangiopathic haemolytic anaemias: fragmented red cells, microspherocytes and spiculated cells.

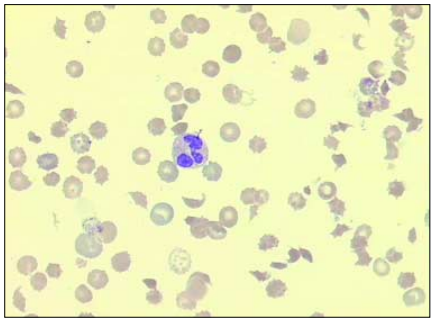

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TABLE 1.
The aetiology of acquired thrombotic thrombocytopenic purpura

Idiopathic
Drugs: quinine, ticlodipine, clopidogrel, heparin, oral contraceptive pill, statins, mitomycin C, immunosuppressive drugs including cyclosporin A, and cytotoxic drugs
Pregnancy and the post-partum period
Infections: human immunodeficiency virus (HIV), mycoplasma, bartonella
Malignancy especially gastric, breast and metastatic disease
Autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis, scleroderma
Transplants: allogeneic bone marrow and solid organ transplants

ogy advice should then be sought in all cases of suspected TTP and platelets should not be given by non-specialists, as this will fuel further platelet aggregation and can cause an abrupt clinical deterioration. Subsequent treatment is emergency plasma exchange, initially of 1 x plasma volume. This removes vWF multimers and anti-protease antibodies, while replenishing vWF cleaving protease. Replacement is with fresh frozen plasma or cryoprecipitate-reduced plasma, which lacks the largest vWF multimers (Blackall et al, 2001). Plasma infusion (30 ml/kg/day) may be beneficial if there is delay in starting plasma exchange, and while adjuvant steroid and antiplatelet therapies are controversial, UK guidelines (British Committee for Standards in Haematology, 2003) recommend giving steroids to all patients and starting low-dose aspirin when the platelet count recovers.

Untreated TTP has a very high mortality (90%), but if treated promptly, up to 90% of patients can make a full recovery. Refractory disease and relapses do occur. HM

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TEACHING POINTS

- Thrombotic thrombocytopenic purpura (TTP) is a treatable condition, but untreated has a 90% mortality.
- Consider TTP in any patient with thrombocytopenia and microangiopathic haemolytic anaemia on the blood film.
- Involve haematology specialists early to help with diagnosis and management and do not give platelets for thrombocytopenia in the meantime.
- Remember that TTP may be accompanied by non-specific influenza-like symptoms, muscular, joint or abdominal pains or neurological signs.
- Remember the conditions associated with TTP.