The haemolytic uraemic syndrome in patients with AIDS

Peter Kelleher, Alison Severn, Charles Tomson, Sebastian Lucas, Jacqueline Parkin, Anthony Pinching, Robert Miller

Objective: Thrombotic microangiopathies have been increasingly recognised in HIV infection. The contribution of haemolytic uraemic syndrome (HUS) has not received as much emphasis as other members of the thrombotic microangiopathies. We describe the clinical features and prognosis of HUS in a group of patients with AIDS.

Setting: St Bartholomew's and The Middlesex Hospitals, London.

Patients: Five HIV seropositive individuals with clinical and histological features consistent with HUS.

Interventions: Blood transfusion, fresh frozen plasma, haemodialysis, renal biopsy, autopsy.

Conclusions: HUS occurs in advanced HIV infection. Hypertension was a prominent clinical feature in HUS in this patient group. Measures to limit renovascular damage were unsuccessful and haemodialysis was usually needed to support renal function. The prognosis is poor, no patient achieved clinical remission and all died.

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Keywords: haemolytic uraemic syndrome; AIDS; HIV; hypertension

Introduction
Renal disease occurs in approximately 10% of AIDS patients. Three principal patterns have been observed in a large European clinico-pathological study: focal glomerulosclerosis, immune complex glomerulonephritis and tubulointerstitial nephritis. Thrombotic microangiopathies have been increasingly recognised in HIV disease with most reports emphasising thrombotic thrombocytopenic purpura rather than haemolytic uraemic syndrome. Here we report five patients with AIDS who developed the haemolytic uraemic syndrome (HUS).

Case 1
A 41 year old Caucasian male homosexual with a history of Pneumocystis carinii pneumonia (PCP), who had completed 16 cycles of vincristine and bleomycin for visceral Kaposi's sarcoma (KS), and pulmonary Non-Hodgkins lymphoma (NHL) was found to be hypertensive (BP 150/110 mmHg), anaemic (Hb 6.8 g/dl) and thrombocytopenic at a routine clinical follow up in December 1992. His fludrocortisone dose for Addison's disease was reduced to 100 µg daily, his azithromycin (AZT) dose was cut to 100 mg bd and a blood transfusion was arranged. Five days later he was admitted with a 24 h history of declining visual acuity. He was noted to be hypertensive (BP 200/115 mmHg) and to have bilateral soft exudates with serous retinal detachments, but no evidence of retinal infection. His medications were zidovudine 100 mg bd, acyclovir 400 mg bd, fansidar one tablet five times a week, fludrocortisone 100 µg daily, hydrocortisone 20 mg bd, and flucnazole 200 mg bd. He gave no history of a recent diarrhoeal illness. An infection screen for bacteria, mycobacteria and fungi was negative in blood, urine and stool. Investigations revealed a microangiopathic haemolytic anaemia, thrombocytopenia, renal failure (table) and normal coagulation studies. His renal function continued to deteriorate over the next four days (serum creatinine level 370 µmol/l) and a renal biopsy specimen showed extensive fibrin thrombi predominantly in the renal arterioles and acute tubular necrosis. Despite blood transfusions, fresh frozen plasma, proscarilycin 7.5 mg/kg/min, adequate antihypertensive therapy (atenolol and nifedipine) he continued to experience recurrent haemolysis and required haemodialysis for renal support. He became pyrexial and neutropenic, aspergillus was isolated on tramsbrial biopsy for which he received amphothercin B. His condition improved over the following weeks; he remained blood transfusion dependent and biochemically stable on twice weekly haemodialysis. The patient was re-admitted in February 1993 confused, hypertensive, hypothermic, and despite supportive measures died within a few hours of arrival. No autopsy was performed.

Case 2
A 40 year old HIV positive white homosexual

Blood pressure and laboratory parameters at diagnosis of HUS

<table>
<thead>
<tr>
<th></th>
<th>case 1</th>
<th>case 2</th>
<th>case 3</th>
<th>case 4</th>
<th>case 5</th>
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<tr>
<td><strong>Age (years)</strong></td>
<td>41</td>
<td>40</td>
<td>38</td>
<td>43</td>
<td>33</td>
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<tr>
<td><strong>BP mmHg</strong></td>
<td>220/115</td>
<td>160/110</td>
<td>170/120</td>
<td>160/120</td>
<td>130/70</td>
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<td><strong>Hb g/dl</strong></td>
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<td>9.1</td>
<td>5.1</td>
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<tr>
<td><strong>Reticulocytes %</strong></td>
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<td>4.4</td>
<td>5.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Blood film</strong></td>
<td>Schistocytes</td>
<td>Schistocytes</td>
<td>Schistocytes</td>
<td>Schistocytes</td>
<td>Schistocytes</td>
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<tr>
<td><strong>Platlets</strong></td>
<td>99</td>
<td>59</td>
<td>18</td>
<td>34</td>
<td>40</td>
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<tr>
<td><strong>CD4 count (10³)</strong></td>
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<td>&lt;10</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td><strong>Creatinine µmol/l</strong></td>
<td>220</td>
<td>420</td>
<td>180</td>
<td>140</td>
<td>340</td>
</tr>
</tbody>
</table>

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man with well controlled cryptosporidiosis was admitted in August 1992 with a history of severe headaches and reduced visual acuity. Physical examination revealed a blood pressure of 160/110 mmHg and bilateral papilloedema. He had anaemia (Hb 10·8 g/dl) thrombocytopenia (101·10\(^6\)/l) and a creatinine of 110 \(\mu\)mol/l. Zidovudine had been discontinued two months previously because of a drug related myopathy. He took regular codeine phosphate and loperamide for cryptosporidiosis. His blood pressure resolved on commencing antihypertensive therapy with captopril. Over the next 6 months he remained well and normotensive, apart from one episode of hypomania treated with thioridazine. Despite stopping captopril his creatinine level continued to rise and a renal biopsy was performed in January 1993. The specimen showed fibrin thrombi in glomerular capillaries and arteriolar occlusion secondary to intimal proliferation. Five days later he was re-admitted with hypertension (BP 240/120 mmHg) and pulmonary oedema. Investigations showed a microangiopathic haemolytic anaemia, thrombocytopenia and renal failure (table) and normal coagulation studies. An infection screen was negative. Despite conventional antihypertensive and diuretic therapy he remained with pulmonary oedema and developed oliguric renal failure. Haemofiltration and fresh frozen plasma was commenced. After two sessions on haemofiltration he refused all further therapeutic interventions and died four days later. No autopsy was performed.

**Case 3**

A 38 year old Caucasian male homosexual, with a previous history of cerebral toxoplasmosis, pneumocystis pneumonia and cryptococcal meningitis was admitted in April 1993 with a one week history of nausea, vomiting and diarrhoea, passing watery stools between three and six times daily. The patient had visited Egypt as a tourist for two weeks returning to the United Kingdom one week prior to admission. His medications on admission were clindamycin 600 mg qid, pyrimethamine 25 mg once daily, carbamezepine 100 mg bd, fucnazoole 600 mg once daily, acyclovir 200 mg tid. Zidovudine 250 mg bd had been stopped six weeks previously because of haematological toxicity and his planned holiday abroad. Physical examination on admission in April 1993 showed that he was pale and hypertensive (BP 170/120 mmHg). Investigations revealed microangiopathic haemolytic anaemia, thrombocytopenia, renal failure (table) and normal coagulation studies. Stool examination and culture were negative for bacterial pathogens and *Clostridium difficile* toxin. The patient was thought to have haemolytic uraemic syndrome. Despite transfusion with whole blood, aspirin 75 mg a day, treatment with fresh frozen plasma, procyclin infusion 7·5 ng/kg/min, haemodialysis was performed as his renal function continued to decline. The patient’s condition stabilised and an initial deterioration in haematological parameters was reversed. However, one month after admission he refused further investigation and treatment. Terminally he had several fits and then died. No autopsy was performed.

**Case 4**

A 43 year old Caucasian homosexual man with a background of recurrent bacterial chest infections, chronic sinusitis and four previous episodes of pneumocystis pneumonia with post PCP bronchiectasis was admitted in December 1993 complaining of generalised tiredness, weakness and low grade fever without sweats. He denied any history of diarrhoea. His current medication was dapsone 100 mg and pyrimethamine 25 mg each three times a week, rotating antibiotics as prophylaxis against recurrent chest infections and prednisolone 10 mg once a day as treatment for myopathy. Zidovudine had been discontinued in March 1993 because of haematological toxicity. General examination was unremarkable. Investigations on admission showed microangiopathic haemolytic anaemia, thrombocytopenia, renal failure (table) and a normal clotting screen. An infection screen was negative. Shortly after admission it was noted that the patient was hypertensive (BP 160/120 mmHg). His renal function continued to deteriorate despite supportive treatment including blood transfusion, fresh frozen plasma and he required haemodialysis. He had several grand mal seizures and became increasingly hypoxic. In view of his advanced HIV disease he was not ventilated. He died and at autopsy there was found bilateral severe alveolar haemorrhage in the lungs, microinfarctions of the heart, brain and pancreas associated with fibrin thrombi in arterioles. The kidneys were large (220 and 225 g) and mottled on cut surface. Histologically, the range of appearances of HUS was seen: fibrin thrombi in glomeruli, glomerular collapse, double-contours of glomerular loops, fibrinoid necrosis of interlobular arteries and afferent arterioles, and acute tubular necrosis (fig 1).

*Figure 1 High power view of a glomerular showing partial collapse, and fibrin thrombi in capillary loops and the afferent arteriole. Martius scarlet blue (MSB) stain. (× 400)*
Case 5
A 33 year old Caucasian homosexual man with a recent history of cryptocsporidial diarrhoea controlled with loperamide PRN was admitted in January 1994. He gave a one week history of passing up to 30 watery pale stools per day with associated cramping lower abdominal pain and anorexia. On admission he was taking co-trimoxazole 900 mg once daily and loperamide as required. Initial examination was unremarkable. Subsequently he became pyrexial (temperature 38°C) and remained normotensive (BP 130/70 mmHg). Admission investigations revealed a haemoglobin of 10.4 g/dl, platelets 68 x 10^9/l, and creatinine 110 μmol/l. Four days after admission repeat investigations showed microangiopathic haemolytic anaemia, thrombocytopenia, renal failure (table) and normal coagulation studies. Despite blood transfusion and daily fresh frozen plasma his blood counts and renal function continued to deteriorate. One day later the patient became increasingly dyspnoeic. His arterial oxygen tension (PaO₂) fell from 8.8 kPa to 5.9 kPa. A chest radiograph showed diffuse interstitial infiltrates. The patient was treated empirically with high dose intravenous co-trimoxazole and methylprednisolone together with erythromycin in order to treat PCP or atypical pneumonia. Over this time his biochemical indices continued to deteriorate (creatinine 491 μmol/l) and his blood counts remained abnormal. Despite respiratory support with continuous positive airways pressure (CPAP) ventilation the patient died. A peri-mortem sputum sample was positive for Cryptococcus neoformans.

At autopsy the patient had disseminated cryptococcosis with involvement of the heart, lungs, liver, pancreas, spleen, lymph nodes, kidneys and adrenals. In addition the lungs showed hyaline membrane disease. The kidneys were large (275 and 330 g) and oedematous on cut section. On histology, there were similar features to case 4, in addition cryptococci were seen in glomeruli (fig 2) and the interstitium.

Discussion
Thrombotic microangiopathies (TMA) are a group of closely related clinical syndromes including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) that are characterised by microangiopathic haemolytic anaemia, thrombocytopenia, intravascular thrombosis and varying degrees of end organ failure. The distinction between TTP and HUS is often made on clinical grounds with the kidney being the organ predominantly affected in HUS, and neurological disease the cardinal feature of TTP. In recent years haemolytic uraemic syndrome has been increasingly recognised in adults and the characteristic thrombotic microangiopathy is more widely distributed in the body than was originally recognised. HUS is a heterogenous group of disorders with two broadly different groups of patients: those with an antecedent history of diarrhoea (D+) and those without (D-). Verocytotoxix producing Escherichia coli is responsible for most cases of D+ HUS and its association with extremes of age and HIV infection suggests that the immune system plays an important role in controlling this infection. D-HUS tends to be sporadic, seen more often in adults and has a poor prognosis with considerable mortality and morbidity from renal failure and hypertension compared to D+ HUS.

The association of thrombotic microangiopathy and HIV has been reported. TTP rather than HUS has been emphasised in most of the case reports. These disorders have been observed much later in the HIV epidemic than other haematological or renal diseases. This may reflect the modification in the natural history of HIV infection due to effective treatment of opportunistic infection and the use of anti-retroviral agents such as AZT.

In contrast to previous reports of TMA in HIV all patients in this series had significant renal impairment with minimal or mild CNS involvement. Even the individual with advanced HIV disease with AIDS diagnoses had no neurological symptoms, and several risk factors for HUS were present including immune dysregulation, drug treatment (bleomycin) and neoplasia (Case 1). A considerable number of infections are associated with HUS including salmonella, shigella, E coli, HIV, Cossachie B, and aspergillus. An antecedent history of diarrhoea following a history of recent foreign travel raised the possibility of shigella or E coli in Case 2 although this was not confirmed. Cryptosporidiosis had been diagnosed within two months of the onset of HUS in two subjects although in both it had been well controlled symptomatically. In the two cases Cryptococcus neoformans played a significant role in this individual’s illness and may have contributed to the aetiology of HUS. A Medline line search for such an association found none. Finally pulmonary aspergillosis was a feature of Case 1’s history. In three subjects AZT had been discontinued in the previous three months or the dose reduced due to...
haematological toxicity. It is unlikely that changes in anti-retroviral therapy triggered the onset of HUS.8,16 Severe hypertension was an early prominent sign in four cases, although the retinal features observed in two individuals were probably secondary to retinal vascular microangiopathy as they failed to resolve despite adequate antihypertensive therapy.17

All patients received standard treatment for anaemia (blood transfusions) and required haemodialysis for renal support. Measures to limit vascular injury such as fresh frozen plasma and prostacyclin failed to arrest disease progression although the efficacy of these treatments remains to be determined.8 Unlike D+ HUS where glomerular thrombosis is the main pathology, intravascular thromboses involving arterioles and small arteries were noted and acute tubular necrosis reflecting extensive vascular occlusion was seen in three of the four cases examined. The outcome was poor, no patient achieved complete remission and all died, which is in agreement with a recent report of TTP and HUS in this infection.18 In contrast other adult groups with HUS in the United Kingdom have a much better prognosis.19 Two requested that all active interventions be discontinued and the remaining patients developed progressive respiratory and other organ failure.

The pathophysiology of HUS is not well established. The most widely accepted view is that endothelial cell injury plays a key role in disease development.20 Direct vascular injury by HIV, fungi and other opportunistic infections could cause endothelial cell damage and trigger HUS.21 Inflammatory mediators such as tumour necrosis factor and reactive oxygen intermediates which are associated with HIV and opportunistic infections have been shown to potentiate verotoxin induced endothelial cell toxicity.12,22 A common epitope may exist between platelet surface glycoprotein receptors and HIV gp 160 protein which could also contribute to further platelet aggregation.24

In conclusion the presence of anaemia, thrombocytopenia, renal impairment and hypertension should prompt clinicians to consider the possibility of HUS in this patient group. Both HIV and secondary opportunistic infections are likely predisposing factors. Our limited experience suggests that HUS in this setting is associated with significant morbidity and a poor prognosis compared with the more widely recognised childhood variant.

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