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CASE REPORT

# The many faces of atypical haemolytic-uraemic syndrome: a diagnostic challenge

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## ABSTRACT

Atypical haemolytic-uraemic syndrome (aHUS) is a rare cause of thrombotic microangiopathy (TMA). The typical form occurs most frequently in children following infection with Shiga-like toxin-producing bacteria, whereas in the atypical form genetic mutations affecting complement regulatory proteins involved in the alternative complement pathway may be identified. The clinical features of aHUS may mimic other causes of TMA such as thrombotic thrombocytopenic purpura and malignant hypertension. We present a case of a 67-year-old woman who presented with a TMA and discuss the diagnostic challenges that were confronted due to the many overlapping clinical and laboratory features of the different causes of this syndrome. Clinicians should be aware of the varied clinical manifestations of TMAs to ensure early diagnosis and initiation of appropriate treatment.

**Keywords:** thrombotic microangiopathy; atypical haemolytic-uraemic syndrome.

## INTRODUCTION

Haemolytic-uraemic syndrome (HUS) is an uncommon cause of thrombotic microangiopathy (TMA) in adults and has a reported overall incidence of 1–2 cases per 100,000 population [1]. It is classified into two types, namely, typical and atypical HUS. The typical form has a reported incidence of 6.2 cases per 100,000 population and frequently occurs in children under 5 years of age when it is caused by Shiga-like toxin-producing bacteria such as *Escherichia coli* O157:H7 [2].

Atypical haemolytic-uraemic syndrome (aHUS) is rare and is reported to represent 10% of HUS cases [2]. It may be familial or sporadic, the latter representing most cases. Triggers include infection with HIV, drugs such as cyclosporin, malignancies and pregnancy and it may follow organ transplantation [3,4]. In half the cases a trigger cannot be identified. In these cases, genetic abnormalities affecting complement-regulatory proteins of an alternative complement pathway may be found.

More common causes of thrombotic microangiopathy, such as thrombotic thrombocytopenic purpura and malignant hypertension, have clinical and biochemical similarities to those of aHUS, making the distinction between these conditions a diagnostic challenge.

We present a case of a 67-year-old woman who presented with TMA and discuss the diagnostic challenges that were confronted as a result of many of the overlapping clinical and laboratory features of the different causes of this syndrome.

## CASE PRESENTATION

A 67-year-old woman, known with schizophrenia for the past ten years, was well controlled on medication, which included intramuscular fluphenazine 12.5 mg monthly, risperidone 0.5 mg daily, promethazine 25 mg daily, and thiamine 100 mg daily. She presented to a peripheral hospital with hyperactive delirium. There was no history of preceding bloody diarrhoea. Her blood

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pressure (BP) was 170/100 mmHg. No obvious source of infection was identified on clinical examination and blood and urine cultures were negative. Routine blood tests revealed features of TMA that included microangiopathic haemolytic anaemia (MAHA) with 20% red blood cell fragments on peripheral smear, haemoglobin concentration of 5.8 g/dL (normal 12.0–15.0 g/dL), lactate dehydrogenase of 1161 U/L (normal 110–210 U/L) and thrombocytopaenia of 54 x $10^9$/L (normal 186–454 x $10^9$/L). She had renal failure with an elevated creatinine of 258 µmol/L (normal 49–90 µmol/L). Other relevant results are shown in Table 1. These laboratory findings, together with her neurological symptoms, were suggestive of thrombotic thrombocytopenic purpura (TTP) and the patient was treated with prednisone (1 mg/kg/day) and fresh frozen plasma (30 units administered over 10 days). She did not show any improvement and was referred to our hospital for further management.

On presentation to our hospital, she had elevated BP of 210/120 mmHg. There were no features of hypertensive target organ damage, and specifically, no flame-shaped haemorrhages, exudates or papilloedema on fundoscopic examination. There were no clinical features suggestive of a connective tissue disease such as systemic lupus erythematosus, scleroderma or anti-phospholipid syndrome. Urine examination showed 2+ protein, 3+ blood and scanty granular casts. A diagnosis of malignant hypertension was made, and she was started on amlodipine 5 mg daily, enalapril 5 mg twice daily and furosemide 80 mg daily.

Despite 2 weeks of good blood pressure control, features of MAHA persisted and the acute kidney injury progressed (Table 1). Investigations to screen for causes of an acute glomerulonephritis were negative except for low concentrations of complement component 3 (C3). The Coombs test and disseminated intravascular coagulation (DIC) screen were also negative, and the vitamin B12 and folate concentrations were in the normal ranges.

She subsequently had a kidney biopsy that revealed a spectrum of thrombotic and angiopathic lesions secondary to endothelial injury (Figure 1). Segmental glomerular necrosis with mesangiolysis and formation of capillary microaneurysms were present. Focal glomerular capillary thrombosis with fragmented erythrocytes (schistocytes) were also seen. The interlobular arteries showed oedematous intimal thickening with luminal narrowing. Immunofluorescence findings were of non-specific granular IgM, C3, IgG and IgA glomerular capillary wall staining. Electron microscopy showed detachment of endothelial cells from glomerular capillary basement membranes with reduplication of the basement membranes. These findings were consistent with a TMA.

**Table 1.** Laboratory results.

| Laboratory test | On admission to peripheral hospital | On admission to referral hospital | Reference range |
|---|---|---|---|
| Sodium | 139 | 136 | 136–145 mmol/L |
| Potassium | 2.8 | 5.4 | 3.5–5.1 mmol/L |
| Urea | 7.1 | 29.3 | 2.1–7.1 mmol/L |
| Creatinine | 135 | 655 | 49–90 µmol/L |
| Leukocyte count | 3.36 | 2.80 | 3.9–12.6 x $10^9$/L |
| Haemoglobin | 8.7 | 4.5 | 12.0–15.0 g/dL |
| Mean cell volume | 89.0 | 107.2 | 83.1–101.6 fL |
| Platelets | 74 | 61 | 186–454 x $10^9$/L |
| Lactate dehydrogenase | 1161 | 705 | 110–210 IU/L |
| Red cell fragmentation | 20 | 11 | 0% |
| Reticulocyte production index | 1.4 | 1.2 | 1–2 adequate response, > 2 suggestive of haemolysis |
| INR | 1.11 | 1.22 | None |
| PTT | 25.3 | 28.4 | 22.0–30.7 sec |
| Fibrinogen | 3.1 | 1.5 | 2.0–4.0 g/L |
| Haptoglobin | < 0.10 | 0.00 | 0.30–2.00 g/L |
| Coombs test | negative | – | |
| CRP | 20 | – | 0–10 mg/L |
| UPCR | 1.54 | 0.28 | < 0.1 g/day |
| ANA | – | negative | |
| C3 complement | – | 0.45 | 0.90–1.80 g/L |
| C4 complement | – | 0.30 | 0.10–0.40 g/L |
| PR3-ANCA | – | negative | negative |
| MPO-ANCA | – | negative | negative |

Abbreviations: INR, international normalized ratio; PTT, partial thromboplastin time; CRP, C-reactive protein; UPCR, urine protein to creatinine ratio; ANA, anti-nuclear antibody; ANCA, anti-neutrophilic cytoplasmic antibody; PR3-ANCA, anti-proteinase 3; MPO-ANCA, anti-myeloperoxidase.

A presumed diagnosis of atypical haemolytic-uraemic syndrome (aHUS) was made. The patient was transferred back to the referring hospital for conservative management due to her overall poor renal prognosis.

## DISCUSSION

This case was a diagnostic challenge, and highlights the overlapping features of some of the thrombotic microangiopathies. Figure 2 shows the overlapping clinical and laboratory features of aHUS, TTP and malignant hypertension.

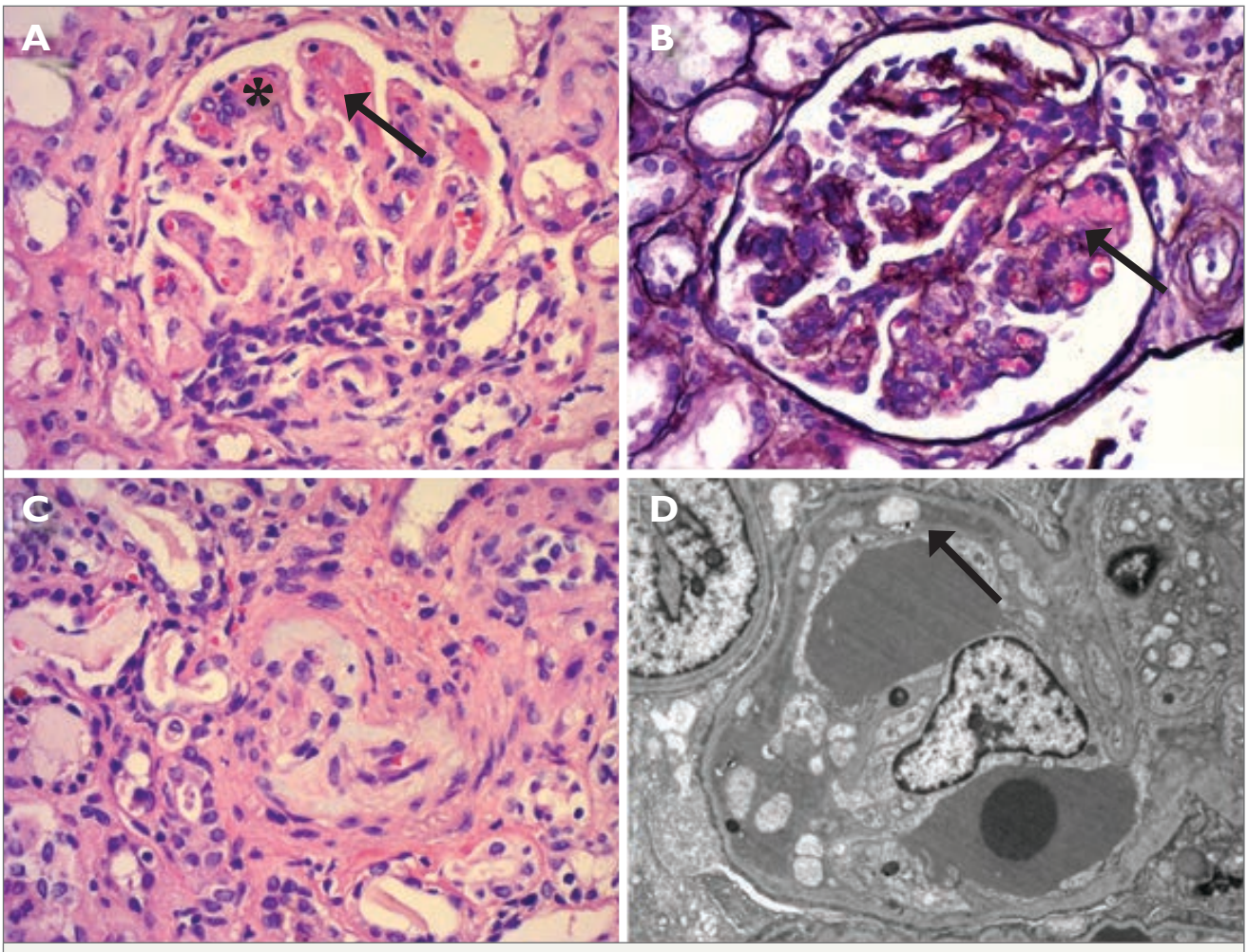


**Figure 1. Histological findings on kidney biopsy.** (A) The glomerulus shows thrombosis (asterisk) and segmental necrosis with mesangiolysis (arrow) (haematoxylin and eosin, x400 magnification). (B) Complete loss of silver positive mesangial matrix in the segment with mesangiolysis (arrow) (Jones methenamine silver, x400 magnification). (C) Oedematous intimal thickening with luminal narrowing of an interlobular artery (haematoxylin and eosin, x400 magnification). (D) Peripheral glomerular capillary loop shows thin, newly formed basement membrane (arrow) on electron microscopy (x5000 magnification).

Our patient was initially diagnosed as having TTP at the peripheral hospital. This was a reasonable conclusion since she had many of the clinical and laboratory features to suggest this diagnosis, such as neurological disturbances (delirium), MAHA, thrombocytopenia and renal failure. TTP remains a relatively common cause of TMA in South Africa, mainly because of the HIV epidemic [5]. Our patient, however, was not HIV infected. Additional features that did not support a diagnosis of TTP included the minimum value of the platelet count and the severity of the acute kidney injury. In TTP patients with severely reduced ADAMTS-13 activity, platelet counts are usually less than 30 x $10^9$/L and the serum creatinine usually does not exceed 200 µmol/L [6]. In many South African hospitals, ADAMTS-13 activity assays are not routinely available and delays in obtaining the results may retard diagnosis and initiation of therapy. In our patient, neither the platelet counts nor the severity of her acute kidney injury supported a diagnosis of TTP.

In addition, her schizophrenia as well as adverse effects related to its treatment may have explained her cognitive impairment. It is also possible that her delirium may have been caused by aHUS itself since up to 20% of patients may have extrarenal involvement, including central nervous system involvement [7].

At our hospital, a diagnosis of malignant hypertension was made initially due to the severity of her hypertension, the ongoing MAHA and the progressive worsening of her acute kidney injury (AKI) despite several days of plasma infusion. Her delirium was thought to be due to hypertensive encephalopathy. Malignant hypertension has recently been defined as extreme elevations of systolic BP (> 220 mmHg) and/or diastolic BP (> 130 mmHg) along with evidence of target organ damage [8,9]. However, the absence of grade III or IV hypertensive retinopathy as well as the ongoing MAHA and progressive AKI, despite tight blood pressure control, made a diagnosis of malignant

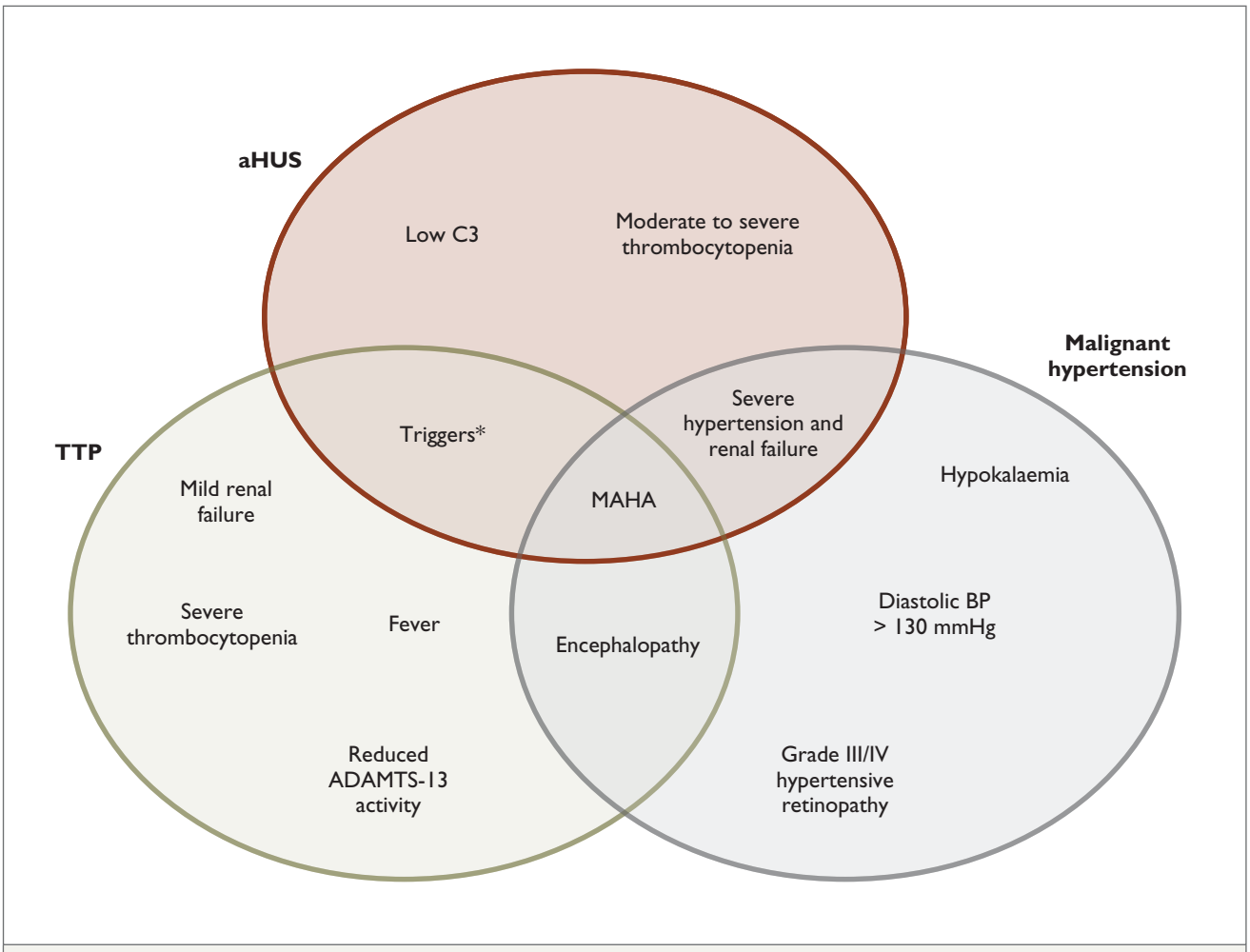


**Figure 2. Venn diagram illustrating the overlapping and the unique features of atypical haemolytic-uraemic syndrome, thrombotic thrombocytopenic purpura and malignant hypertension.**
Abbreviations: aHUS, atypical haemolytic-uraemic syndrome; TTP, thrombotic thrombocytopenic purpura; MAHA, microangiopathic haemolytic anaemia; ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; BP, blood pressure.
*Triggers include HIV infection, malignancy, pregnancy, autoimmune disease and drugs.

hypertension unlikely. The mild degree of proteinuria also made acute glomerulonephritis unlikely as an underlying cause of malignant hypertension.

We considered the diagnosis of aHUS with severe hypertension. A case series of aHUS included 9 patients with severe hypertension and renal TMA [10]. All patients had mild to moderate hypertensive retinopathy but just one had papilloedema. This patient had the highest BP (240/150 mmHg). The mean age of these patients was 39 years (range 27–65 years), 56% were female and average BP was 203/123 mmHg. The mean serum creatinine was 837 µmol/L (range 162–1730 µmol/L), 78% had haematuria and mean protein excretion was 1.7 g per day (range 0.4–3.9 g per day). Average haemoglobin was 6.5 g/dL (range 5.1–8.2 g/dL), average LDH was 875 U/L (range 165–2125 U/L), 44% had MAHA and the average platelet count was 190 x $10^9$/L (range 98–340 x $10^9$/L). All patients had identifiable abnormalities involving complement. The key message from this paper is that patients presenting with severe hypertension and renal TMA may be misdiagnosed with malignant hypertension, concealing the true diagnosis of aHUS. The authors recommended that all patients with severe hypertension and renal TMA be investigated for an underlying complement disorder.

Malignant hypertension with renal TMA and aHUS with severe hypertension are likely to be two distinct clinical entities [11]. The clinical findings of grade III or IV hypertensive retinopathy, diastolic BP > 130 mmHg and a good response to BP control distinguishes malignant hypertension from aHUS [11]. The genetic abnormalities of the alternative complement pathway found in aHUS have very rarely been identified in patients with malignant hypertension [11]. Whether genetic mutations of the alternative complement pathway are the initiating event in these cases,

or are merely activated in response to shear stress caused by severe hypertension, remains to be answered.

The diagnosis of aHUS was strongly suspected after the finding of low serum C3 with normal C4, which indicated activation of the alternative complement pathway. The kidney biopsy was performed to seek additional evidence in support of the diagnosis since tests to identify genetic mutations affecting complement regulatory proteins are currently unavailable in South Africa. The histological findings of mesangiolysis, glomerular capillary intraluminal thrombosis and microaneurysm formation, immune complex deposition along the glomerular capillary wall and endothelial cell detachment were similar to those reported by Timmermans et al. [10].

Treatment of aHUS involves intensive plasma exchange with 1–2 plasma volume exchanges recommended daily and should be initiated within 24 hours of diagnosis [12]. Additional therapies include steroids, azathioprine, mycophenolate mofetil and rituximab. Response to therapy is dependent on the type of complement abnormality involved. Studies that used plasma exchange reported short-term remission rates ranging from 30–80%; however, remission was defined as haematological remission but with renal consequences that included end-stage renal disease [1]. Reported rates of end-stage renal disease are 60–70%. In patients that receive kidney transplants, as many as 50% experience recurrence in the allograft with 80–90% developing graft failure [1]. Given the high cost of plasma exchange, the high rate of end-stage renal disease with dialysis-dependence and the high rate of renal allograft recurrence and graft failure, a decision was made to manage the patient conservatively.

## CONCLUSIONS

Atypical HUS may mimic other causes of TMA, particularly TTP and malignant hypertension. It is therefore important that clinicians are aware of the varied clinical presentations of these TMAs to ensure early diagnosis and the initiation of appropriate treatment.

### Ethical considerations

Approval for publication was granted by the Health Research Ethics Committee of Stellenbosch University (reference number C19/03/008).

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