

Clinical dilemma in the treatment of a patient with microangiopathic haemolytic anaemia, thrombocytopenia and severe hypertension

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ABSTRACT

While haemolytic uraemic syndrome in children is predominantly associated with Shiga toxin-producing *Escherichia coli* (typically 0157:H7), some cases occur without associated diarrhoea, or as the manifestation of an underlying disorder other than infection. Haemolytic uraemic syndrome is characterised by microangiopathic anaemia, thrombocytopenia and renal failure, on occasion accompanied by severe hypertension. Malignant hypertension is a syndrome that sometimes exhibits the same laboratory abnormalities as haemolytic uraemic syndrome as it may share the same pathological findings: thrombotic microangiopathy. As clinical features of both entities overlap, the distinction between them can be very difficult. However, differentiation is essential for the treatment decision, since early plasma exchange dramatically reduces mortality in haemolytic uraemic syndrome not associated with diarrhoea. An increasing number of genetic causes of this pathology have been described and may be very useful in differentiating it from thrombotic microangiopathy due to other aetiologies. Despite advances in the understanding of the pathophysiology of haemolytic uraemic syndrome not associated with diarrhoea, the management often remains empirical. We describe a patient with simultaneous microangiopathic haemolytic anaemia, thrombocytopenia and severe

hypertension managed in the acute period of illness with plasma exchange.

Key-Words:

ADAMTS₁₃ (a desintegrin-like and metalloprotease with thrombospondin type I repeats); complement regulation factors; malignant hypertension; microangiopathic haemolytic anaemia; plasma exchange; thrombotic microangiopathy.

INTRODUCTION

Thrombotic microangiopathy (TMA) is a pathological finding characterised by arteriolar fibrinoid necrosis, intimal thickening and media proliferation with resultant luminal narrowing leading to excess fragmentation of erythrocytes and consumption of platelets¹⁻³. Laboratory findings of TMA include microangiopathic haemolytic anaemia and thrombocytopenia and elevation of serum lactate dehydrogenase^{1,4-6}. TMA, while typically associated with Haemolytic Uraemic Syndrome (HUS), can however occur in association with other conditions, including malignant hypertension, sepsis, Systemic Lupus Erythematosus, systemic sclerosis and malignant disease^{1,7-9}. HUS is the consensual term for children who meet the diagnostic criteria of thrombocytopenia

and microangiopathic haemolytic anaemia along with renal failure. Thrombocytopenic thrombotic purpura (TTP) is reserved for the rare children who present with these laboratory findings but without renal failure or for patients with congenital deficiency of ADAMTS13 (“a desintegrin-like and metalloprotease with thrombospondin type I repeats”) activity⁶. These definitions and syndrome classification are still the subject of debate. Typical HUS is the main cause of renal impairment in young children and is caused by verocytotoxin (shiga-like toxin)-producing bacteria, usually by enterohaemorrhagic *Escherichia coli* serotype O157:H7 and is associated with prodromal diarrhoea (it is also known as typical HUS, diarrhoea associated HUS or D+HUS) although other serotypes and even other bacteria may be responsible for this entity⁷. Supportive therapy and control of infection are prescribed in these cases. All remaining HUS cases, commonly referred to as atypical HUS, imply a thorough investigation which will reveal a risk factor in more than half the cases (Table 1)⁹. Disorders of complement regulation account for the majority of cases but other genetic or acquired abnormalities may present initially as TTP-HUS, such as deficiency of the enzyme ADAMTS13, a specific protease that cleaves multimeric von Willebrand protein and may be decisive in therapeutic management^{3,4,6-9}. Plasma exchange substantially reduces the mortality in these

situations from 90% to 10%^{4,6}. The authors report the case of a patient with microangiopathic haemolytic anaemia, thrombocytopenia and renal impairment associated with severe hypertension, which made the differential diagnosis and therapeutic approach difficult.

■ CASE REPORT

A healthy five-year-old Indian boy, resident in Portugal for three years, began to have complaints of morning vomiting lasting for one to three days, sometimes accompanied by frontal headache, which prompted several health centre visits about three months before hospital admission. In the week before admission he was evaluated in the emergency room for vomiting and facial palsy. His brain CAT scan showed bilateral lenticular hypodensities and he was symptomatically medicated with paracetamol and ibuprofen and referred for a Neurology consultation. One week later he was admitted with incoercible vomiting. He had no fever, diarrhoea or other complaints. At the time of admission the physical examination revealed a very ill boy with right facial palsy, pallor, jaundiced sclerotic, cardiac systolic murmur II / VI, normal lung auscultation, painless abdomen with no organomegaly or murmurs, no signs of haemorrhagic discrasia, dehydration, fever or respiratory distress. His BP was 238/134mmHg. Laboratory investigation revealed haemoglobin 13.6g/dl and a platelet count of 109,000/l, reticulocyte count 2.95%, mild renal insufficiency (GFR 61ml/1.73m²/min), mild unconjugated hyperbilirubinaemia (total bilirubin/direct bilirubin 1.48/0.58 mg/dl) and serum lactate dehydrogenase 1011mg/dl. Spherocytes and schistocytes were found in a peripheral blood smear. Large amounts of haemoglobin, proteins and glucose were present in his urine. There were no changes in coagulation and liver tests. The blood and urine cultures performed were all negative. Abdominal ultrasound was normal and renal ultrasound showed absence of renal parenchymal-sinus differentiation. Chest X-ray showed a nonspecific bilateral interstitial infiltrate and a slightly increased cardiothoracic index. Brain angiography MR showed “multifocal lesions involving mainly the nuclei of the grey base and the bulb, with no obvious signs of brain arteritis or acute/subacute ischaemia or

Table 1

Classification of HUS, TTP, and related disorders³

- 1. Aetiology advanced**
 - 1.1. Infection induced**
 - 1.1.1. Shiga and shiga-like toxin-producing bacteria: Enterohaemorrhagic *Escherichia coli*, *Shigella dysenteriae* type 1, *Citrobacter freundii*
 - 1.1.2. *Streptococcus pneumoniae*
 - 1.2. Disorders of complement regulation**
 - 1.2.1. Genetic
 - 1.2.2. Acquired
 - 1.3. Defective cobalamin metabolism**
 - 1.4. Quinine induced**
- 2. Clinical associations: aetiology unknown**
 - 2.1. HIV infection**
 - 2.2. Malignancy, cancer chemotherapy, ionising radiation**
 - 2.3. Calcineurin inhibitors and transplantation**
 - 2.4. Pregnancy HELLP syndrome, contraceptive pill**
 - 2.5. Systemic lupus erythematosus, anti-phospholipid antibody syndrome, systemic sclerosis**
 - 2.6. Glomerulopathy**
 - 2.7. Familial not included in level 1**
 - 2.8. Unclassified**

bleeding". The EEG, cardiology and ophthalmology evaluations were normal. The immunology parameters (C3, C4, CH100, antinuclear antibody ANA, anti double stranded DNA antibody anti-dsDNA, circulating immunocomplexes CIC, anti-extractable nuclear antigen anti-ENA, lupus anticoagulant LA, anti-cardiolipin antibody ACL and antiphospholipidic antibody) were all negative. The functional study of the thyroid and suprarenal glands (active renin, aldosterone, serum and urinary catecholamines, metanephrin and nor-metanephrin and vanilmandelic acid) showed no changes. Serologies for HIV and Hepatitis B virus were negative. ADAMTS13 activity was 89% (normal range (NR) 40-130%), the ADAMTS13 antigen was 57% (NR 70-160%) and the anti-ADAMTS13 antibody was 1U/ml (NR <15 U / ml). Definitive results from serum and genetic analysis of complement regulatory factors H, I, MCP or CD46 were not available as the first blood samples had technical issues that made laboratory investigation impossible and, in the meantime, the child returned to India. Treatment with infusion of labetalol (0.5 mg/kg/h to 2mg/kg/h) and nifedipine for 24 hours followed by oral antihypertensive therapy with nifedipine (0.9 to 1.8 mg/kg/day) and enalapril (0.2 to 0.5 mg/kg/day), resulted in significant improvement of blood pressure with normalisation in the second week of admission. As he remained symptomatic (vomiting, abdominal pain, prostration and headache) along with a rapidly progressive worsening of the intravascular haemolysis and renal failure

(Hb 11.4g/dl, Htc 30.2%, reticulocytes 4.95%, haptoglobin <0.08g/l, platelets 105,000/ μ l, GFR 41.9ml/mn/1.73m²), plasma exchange was initiated (1 volume per session) and three cycles were performed. There was a remarkable clinical and biochemical improvement after the start of plasma exchange, with a remaining complaint of sporadic abdominal pain only that disappeared on the third day of treatment. Table II shows laboratory findings and therapeutic approach during the first week of hospital stay. Diuresis and weight remained normal during his hospital stay and there was a single episode of high temperature (38°C) during the last plasma exchange session, with negative blood cultures. The renal ultrasound repeated on the 15th day of admission showed the same changes as on admission. He was discharged on the 21st day of admission, clinically well, with persistence of his facial palsy and normal BP under oral treatment with enalapril and nifedipine. A renal biopsy was performed 65 days after the acute episode and showed a morphological pattern of interstitial fibrosis with inflammatory infiltrate of mononucleated cells around atrophic tubules in more than half of the cortex as well as arteriolar media hypertrophy and intima fibrocellular thickening with marked reduction or total occlusion of the lumen and arterial media hypertrophy. As of the fifth month of hospital discharge, he remains clinically well with only a slight/moderate facial palsy and blood pressure around 100/57mmHg.

Table II

Clinical and laboratory evolution and therapeutic approach during the first week of hospital stay

Day of hospital stay	1st	3rd	4th	5th
Laboratory findings	Hb 13.6 g/dL Platelets 109 000/ μ L Reticulocytes: 2.95% GFR: 61mL/mn/1.73m ² Blood smear: Spherocytes and schistocytes	Hb 11.3 g/dL Platelets 105 000/ μ L Reticulocytes: 4.95% GFR: 41.9 mL/mn/1.73m ² Haptoglobin <0.08g/L Blood smear: Spherocytes and schistocytes	Hb 11.5 g/dL Platelets 159 000/ μ L Reticulocytes: 4.63% GFR: 47.9mL/mn/1.73m ² Haptoglobin <0.08g/L Blood smear: Rare spherocytes and schistocytes	Hb 11.5 g/dL Platelets 227 000/ μ L Reticulocytes: 3.48% GFR: 47.9mL/mn/1.73m ² Haptoglobin: 0.77g/L Blood smear: Rare spherocytes and schistocytes
Mean blood pressure	220/135 mmHg	131/64 mmHg	142/75 mmHg	147/92 mmHg
Treatment	Infusion of labetalol (0.5 mg/kg/h to 2mg/kg/h) and nifedipine followed by oral therapy with nifedipine (0.9 to 1.8 mg / kg/day) and enalapril (0.2 to 0.5 mg/kg/day)	Plasmapheresis Oral nifedipine (0.9 to 1.8 mg/kg /day) Oral enalapril (0.2 to 0.5 mg/kg/day)	Plasmapheresis Oral nifedipine (0.9 to 1.8 mg/kg/day) Oral enalapril (0.2 to 0.5 mg/kg/day)	Plasmapheresis Oral nifedipine (0.9 to 1.8 mg/kg/day) Oral enalapril (0.2 to 0.5 mg/kg/day)

■ DISCUSSION

After sudden onset of intravascular haemolysis and thrombocytopenia along with severe hypertension, renal and neurological compromise, with no reference to diarrhoea, drugs or toxic ingestion and a negative infectious and immunologic investigation, the differential diagnosis focused mainly between D- HUS and malignant hypertension^{7,9}. The diastolic values higher than 130 mmHg and the only mild thrombocytopenia favoured the diagnosis of malignant hypertension, but this hypothesis seemed less likely, given the absence of previous hypertension and the lack of impact on the usual target organs (normal ophthalmology and cardiology examinations)². According to the literature, the first-line treatment for HUS not linked to diarrhoea is plasma exchange which significantly reduces mortality (from 90% to 10-30%) when promptly instituted^{1-3,7,10,11}. This evidence explains the decreased stringency of criteria for the diagnosis of HUS and thrombocytopenia and microangiopathic haemolytic anaemia without identifiable cause are sufficient for making this diagnosis and starting plasma exchange^{3,7,9}. Sometimes, as with this child, anaemia is not immediately apparent but this should not delay the institution of therapy, if other laboratory signs of haemolysis are present, such as the evidence of erythrocyte fragmentation³. In the context of microangiopathic anaemia with thrombocytopenia along with severe hypertension, some authors suggest that plasma exchange should be performed in all patients with moderate to severe forms of thrombocytopenia accompanying microangiopathic anaemia (platelets 20,000-50,000/ μ l)² as most of the reported cases of thrombocytopenia due to malignant hypertension have platelet counts of more than 50,000/ μ l^{12,13}, although there are some exceptions^{14,15}. Nonetheless, recent articles show that TMA may be present with substantial renal injury in the presence of normal values of platelets¹⁰. More studies to determine the usefulness of plasma exchange in these atypical thrombocytopenic forms of TMA are necessary. As serum analysis of ADAMTS13 and von Willebrand multimers was not ready and as there was laboratory worsening of the microangiopathy and renal failure despite aggressive arterial pressure control, we felt the need for medical intervention other than blood pressure control and started daily sessions of plasma exchange with fresh frozen plasma (one plasma volume)^{3,11}. Clinical

and biochemical improvement following the institution of plasma exchange does not, however, rule out malignant hypertension since antihypertensive therapy was given simultaneously and blood pressure control seems to be sufficient for the remission of the clinical picture observed in malignant hypertension². However, by this time, the hypertension was not totally controlled (BP>P95). A normal ADAMTS13 result does not allow confirmation of diagnosis and obviate the determination of von Willebrand factor multimers which are cleaved by this protease¹⁰. Neither the changes in the brain MR nor angiography MR were specific to any of the diagnoses in question. Indeed, the histological examination of the biopsy was frankly suggestive of TMA but the morphological findings were not specific of either of the two clinical entities. Serum and genetic analysis of complement factors would be very useful for a possible confirmation of the diagnosis of D- HUS and ensuing treatment of the patient^{3,7}.

■ CONCLUSION

As described in this patient, microangiopathic haemolysis accompanied by severe hypertension makes a timely diagnosis extremely difficult to establish. The evidence of reduced mortality in patients with D- HUS treated promptly with plasma exchange and the laboratory worsening in our child despite mild thrombocytopenia and aggressive blood pressure control seemed to justify our therapeutic decision. Moreover, any delay in performing plasma exchange may reduce its efficacy. The reduced activity of ADAMTS13 as well as abnormalities in complement regulation is useful in the differential diagnosis but the results were not ready for a timely decision. The absence of such changes does not rule out the diagnosis, since other pathogenic mechanisms are described and many cases of D- HUS are idiopathic.

The diagnosis of D- HUS is often presumptive, which makes the decision to initiate plasma exchange very difficult. There are currently no data demonstrating the effectiveness of any therapeutic modality beyond plasma exchange. Future research should address these aspects³.

Conflict of interest statement. None declared.

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