Early recognition and access to terminal complement blockers in patients with atypical HUS significantly improves their outcome: a case report

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Keywords

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Abstract

A 7-year-old boy presented with fever, pruritus and petechiae. Laboratory analysis revealed haemolytic anaemia with presence of schistocytes, thrombocytopenia and acute kidney injury, diagnostic for a thrombotic microangiopathy (TMA). Given the severe clinical presentation, the lack of evidence for verotoxin positive TMA and a normal ADAMTS13, treatment with eculizumab was started. This resulted in a complete resolution of the TMA course with recovery of the kidney injury. Workup revealed high titre of anti-factor H antibodies, diagnostic for an atypical haemolytic uremic syndrome (aHUS). This case demonstrates that early recognition and treatment of TMA is essential to optimize the outcome of these patients.

Background

Thrombotic microangiopathies (TMA) are a group of rare disorders characterized by microangiopathic haemolytic anaemia, non-immune thrombocytopenia, and organ dysfunction (1-4). Early diagnosis and treatment of TMA to prevent end organ damage has a high impact on the outcome and prognosis of these patients (3). This is especially true for the subgroup of children with atypical haemolytic uremic syndrome (aHUS), where dysregulation of the alternative complement pathway is involved (5-7). Early access to the terminal complement inhibitor eculizumab has drastically improved the prognosis of these vulnerable patients (1, 7). This case report describes a patient with aHUS who received successful treatment with eculizumab early in the course of the disease.

Case description

A previously healthy 7-year-old boy consulted the general paediatrician with fever, pruritus and cough. Physical examination revealed normal cardiocirculatory parameters and normal neurological status. Skin inspection during clinical examination revealed multiple petechiae on the upper body, together with some scratches. High normal blood pressure was noted with systolic values ranging between the 90th and 95th percentile. Other vital signs were unremarkable and there was no history of oliguria or anuria. Laboratory analysis revealed thrombocytopenia of 68 000/µL (reference range, 205 000 – 450 000/µL), haemoglobin of 11,5 g/dL (reference range, 11,3 – 14,2 g/dL) and an elevated lactate dehydrogenase (LDH) titre of 822 U/L (reference range, 120 – 300 U/L). Since several family members had an upper respiratory tract infection in the week prior to the patients' symptom onset, a working diagnosis of post-viral thrombocytopenia was presumed. The patient was subsequently sent home from the outpatient clinic.

However, the following day the patient returned to the clinic with worsening pruritus and petechiae, and new-onset vomiting. Laboratory analysis revealed haemolytic anaemia: haemoglobin 10,3 g/dL, LDH 1288 U/L and haptoglobin < 0,1 g/L (reference range, 0,3 – 2,0 g/L) with the presence of schistocytes. He also had thrombocytopenia (33 000/µL) and acute kidney injury with creatinine value of 1,28 mg/dL (reference range, 0,29 – 0,47 mg/dL), diagnostic for TMA. The boy was admitted to the paediatric intensive care unit for monitoring and initiation of treatment.

Timeline and interventions

Given the absence of an episode of bloody diarrhoea preceding this acute episode of TMA, as would be suspected in typical haemolytic uremic syndrome (HUS), an aetiological workup for atypical HUS was initiated. ADAMTS13 (also known as von Willebrand factor-cleaving protease) level was normal (0,79 IU/mL with reference range of 0,4 – 1,3 IU/mL), the Coombs test was negative and no Shiga toxin could be detected in serum and repeated stool samples (by culture and PCR). Complement levels were low to normal: complement component 3 (C3) was 0,729 g/L (reference range, 0,680 – 1,270 g/L) and C4 was 0,17 g/L (reference range, 0,230 – 0,470 g/L). Additional tests revealed low alternative pathway 50 (AP50) levels of 21% (reference range, 30-113%) but normal total haemolytic complement (90% with reference range between 69 and 129%). At the time of diagnosis, the boy's blood pressure was 114/83 mmHg (between 95th and 99th percentile). This remained fairly stable during admission, although the patient's renal function deteriorated (peak creatinine level of 8,32 mg/dL) and he subsequently developed signs of uremic encephalopathy. As initial investigations were negative for Shiga toxin-associated *Escherichia coli* haemolytic uremic syndrome (STEC-HUS) and TTP (thrombotic thrombocytopenic purpura), he received a first dose of eculizumab after vaccination against *Neisseria meningitidis* serogroups A, B, C, W and Y (with *Menveo®* and *Bexsero®*) and initiation of antibiotic prophylaxis. Initially third generation cephalosporins were given intravenously, but after 4 days the patient was switched to oral amoxicillin. Eculizumab was administered 10 days after the boy's initial presentation. The patient was on supportive care only until the first dose of eculizumab. Two days after eculizumab administration, the patient was started on peritoneal dialysis.

Following his first eculizumab infusion a marked clinical and biochemical improvement was observed. Figure 1 clearly shows that thrombocytopenia and haemolysis parameters recovered within 30 days. Due to a significant improvement in renal function, peritoneal dialysis could be discontinued seven days after treatment initiation (figure 1). On day 23 of hospitalisation, the patient was discharged while maintained on eculizumab.

Subsequent results showed high levels of anti-complement factor H (CFH) antibodies (titre: 19 584 arbitrary units (u Arb), normally < 150 u Arb) with only 27% of factor H activity (reference range, 78-108%), confirming the diagnosis of aHUS. In addition, genetic analysis detected a homozygous deletion of CFHR1 and CFHR3.

One month after the first infusion of eculizumab, corticosteroids and mycophenolate mofetil were added to treat the autoimmune basis of the disease, resulting in a decrease in anti-CFH antibody titre (< 200 UAb) two months later.

12 months after initial presentation, the patient has an excellent renal outcome with a normal glomerular filtration rate (GFR), no proteinuria and normal blood pressure while on a low dose of angiotensin-converting enzyme (ACE) inhibitors.

Discussion

TMA consists of a triad of microangiopathic haemolysis, thrombocytopenia and evidence of endothelial cell damage leading to a life-threatening systemic disease characterized by acute kidney injury, neurological or gastrointestinal complications with high morbidity and mortality (figure 2) (2, 3, 5). Shiga toxin-associated haemolytic uremic syndrome (STEC-HUS), thrombotic thrombocytopenic purpura (TTP) and atypical HUS (aHUS) are the most important disorders within the TMA group (5). Differentiation between these three disorders must be made, which can be done with verotoxin screening (culture or PCR) to exclude STEC-HUS and ADAMTS13 diagnostics for TTP. The distinction between these diseases is important because of the need for different therapeutic approaches: i.e. supportive therapy for STEC-HUS versus plasmapheresis for TTP (2, 5, 6). In children, aHUS must always be considered in previously healthy patients with HUS who have no evidence of STEC-HUS and a normal ADAMTS13 activity (2, 8). In addition to STEC, other infectious causes such as *Streptococcus pneumoniae* or viral agents (e.g. HIV, influenza, hepatitis B or C, etc.) can cause TMA and always have to be considered. In patients with comorbidities, TMA can be associated with the co-morbid condition itself, for example in patients with malignancies or those who have undergone haematopoietic stem cell transplantation. Autoimmune diseases, malignant hypertension, pregnancy, cobalamin C deficiency and some drugs (e.g. cocaine) are also known to trigger TMA (3, 9).

In the paediatric population, STEC-HUS (also previously called “typical HUS”) is the most prevalent underlying cause of TMA. Hallmark in the pathophysiology of STEC-HUS is the production of verotoxin by an infectious pathogen (most commonly *Escherichia coli*) in the gut. After absorption of verotoxin from the gut into the circulation, verotoxin is translocated to the microvascular endothelial cells making it responsible for renal and colonic endothelial cell injury. This stimulates the generation of thrombin and the deposition of fibrin in the microvasculature. The concentration of PAI-1 (Plasminogen Activator Inhibitor 1) rises, which blocks fibrinolysis, exacerbating the thrombotic injury (10). Typically, patients with STEC-HUS present with fever and bloody diarrhoea. In the majority of patients these symptoms occur in the early phase, with a typical complaint free interval before the TMA, but are not required for diagnosis. Additionally, the central

Figure 1: Evolution of laboratory findings, illustrating creatinine, haemoglobin, LDH and thrombocyte values according to treatment.
RPC: red packed cell transfusion; PD: peritoneal dialysis; MMF + P: mycophenolate. mofetil + prednisolone.

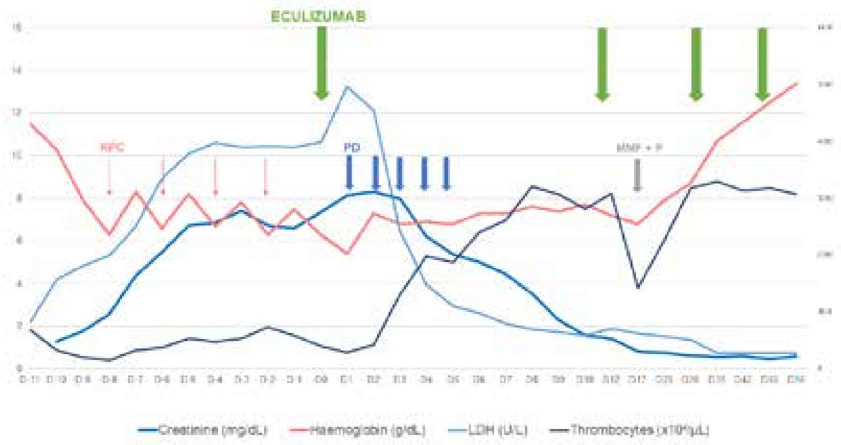
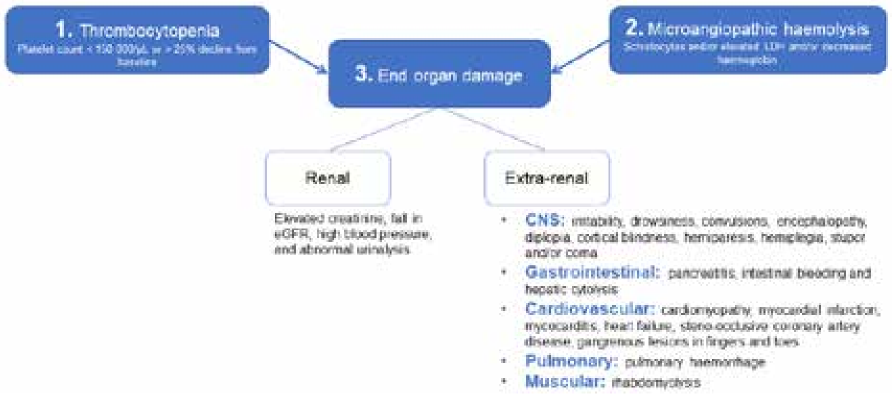


Figure 2: Visualisation of the triad of TMA with clinical and biochemical manifestations (3,5).
CNS: central nervous system.



nervous system, pancreas and other organs can be affected by the Shiga toxin, which explains the clinical variability of STEC-HUS (3).

In contrast, atypical HUS (aHUS) is a rare cause of TMA, characterized by a loss of control of especially the alternative pathway of the complement, which will also result in the classical triad of TMA (1, 3). The most important regulators of the alternative complement pathway are complement factor B (CFB), factor H (CFH), factor I (CFI), membrane cofactor protein (MCP) and thrombomodulin (3, 5, 8). About 65% of patients with aHUS carry mutations in complement genes that result in the loss of protection from formation of the membrane attack complex and eventually in TMA lesions (4). Production of anti-CFH antibodies as presented in this case, also causes an overactivation of the alternative complement pathway, leading to the pathogenesis of aHUS (1, 5). The presence of anti-CFH antibodies is strongly associated with a genomic homozygous deletion of *CFHR1* and *CFHR3*, which was also the case in our patient (1, 2, 6, 9). Kavanagh et al. suggest that a deficiency of CFHR1 is a predisposing factor in the development of autoantibodies (1). Although not all patients with *CFHR1* deletion will display anti-CFH antibodies. According to Raina et al., nearly 10% of the patients with anti-CFH antibodies do not show a deletion in *CFHR1* (11). Studies show that between 21% and 25% of patients presenting with aHUS have CFHR deletions (1, 5). The incidence of these CFHR deletions varies regionally, for example in a South-Korean study 29% of children with aHUS had a homozygous deletion in the *CFHR1* gene and 73% of patients with anti-CFH antibodies had this deletion (2). The homozygous deletion of *CFHR1-R3* is a polymorphism carried by 2-9% of Europeans, 16% of Africans and less than 2% of Chinese people (6).

Eculizumab is a humanized monoclonal IgG antibody that inhibits C5 cleavage and thus the generation of the pro-inflammatory molecule C5a and the formation of the cell membrane attack complex preventing downstream effects of overactivation of the alternative complement pathway efficiently (5, 6, 12). Most recent studies show a complete TMA response in 50-85% of the patients with aHUS (5). Before the availability of eculizumab, prognosis of aHUS was poor, with 30-50% of children developing renal failure stage 5, high relapse after transplantation and a total mortality rate of 8-25% (7, 12). Two decades ago, the gold standard for management of aHUS was plasma exchange, aiming to replace the non-functioning complement proteins and remove the CFH autoantibodies out of the circulation. Unfortunately, in children, the complication rate of plasma exchange is high. Liver transplantation was also considered in the past, especially in patients with CFH mutations, although studies showed limited success with a lot of perioperative morbidities. Donor shortage also makes this a less favourable option. Given the high cost of eculizumab, plasma exchange is still the only available option in low-income countries (1, 2).

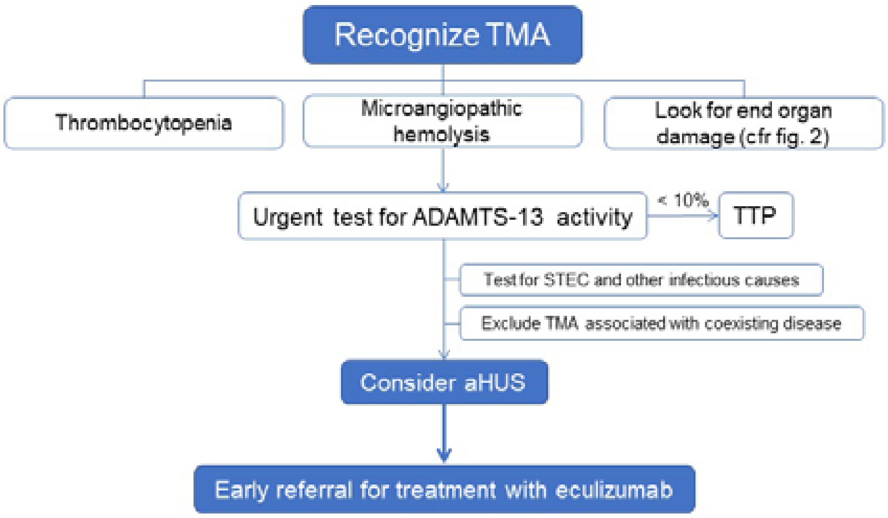
The introduction of eculizumab has significantly improved the outcome of patients with complement mediated aHUS. In the 2016 international consensus approach it is suggested to use eculizumab as first-line treatment in children with a suspicion of aHUS (6). The existence of a window-of-opportunity has also been demonstrated, with earlier treatment initiation leading to a better renal outcome (1, 6, 8). Patients receiving eculizumab should be immunised against meningococcal and pneumococcal infections, as the use of eculizumab implies a hampered immune response to encapsulated bacteria (4, 7, 12).

Initially, life-long treatment with eculizumab was claimed, but there is increasing evidence that there might be several subtypes where discontinuation of therapy after six months is defendable. The highest relapse rates after interruption of therapy are in patients with factor H mutations (1, 6, 9). After the initial treatment with eculizumab in patients with an autoimmune form of aHUS, long-term immunosuppressive treatment should be initiated to maintain a reduced level of anti-CFH antibodies and to prevent relapses, allowing to stop eculizumab (8). In our case the association of corticosteroids and mycophenolate mofetil led to a favourable decline in the anti-CFH antibody titre. With the observed immediate and persistent recovery from dialysis, our case confirms that eculizumab is efficient in patients with aHUS with severe renal involvement.

Nevertheless, eculizumab is widely accepted as a highly effective therapy for children with aHUS. The downside of this therapy is the need for intravenous administration every two weeks often over a long period of time, which has a major impact on the child's quality of life: frequent veinpunctures and hospital visits, frequent absences from school, etc. New complement inhibitors with longer treatment intervals and/or subcutaneous administration (i.e. ravalizumab and crovalimab), allowing administration at home are on their way to tackle the burden of the current therapy (13, 14). In addition to the psychosocial impact of treatment with eculizumab, this therapy remains a very expensive drug that imposes a high financial burden on society. To date, the drug is not available in all countries and initiatives are needed to both improve equitable access of this therapy worldwide and to guarantee that is it used in the correct indications (15).

Although aHUS is a rare disorder in the paediatric population, every paediatrician should be aware of the disease when a patient presents with TMA, especially if a non-STEC-HUS is likely. Early recognition and screening for this condition is essential to maximise the outcome of these children, especially in the current era of life-changing biologic treatments such as eculizumab. With this case report, we would like to highlight the importance of an early referral of the patient to a specialised centre in parallel with an early initiation of TMA diagnostic work-up (figure 3). Early referral and diagnosis will promote early

Figure 3: Diagnostic algorithm for patients presenting with thrombotic microangiopathy. Urgent testing for TTP (with ADAMTS13 activity) is critical and should be done within 72 hours after diagnosis (3,8). *TMA = thrombotic microangiopathy; STEC = Shiga toxin-producing Escherichia coli; aHUS = atypical haemolytic uremic syndrome.*



access of those patients with non-STEC-HUS to specialised treatment such as plasmapheresis and eculizumab and to expertise in metabolic diseases and others. Therefore, we recommend prompt contact with TMA reference centres upon diagnosis of TMA and urgent diagnostic screening within 72 hours of diagnosis of TMA for STEC-HUS and other types of post-infectious TMA, TTP and secondary forms of TMA (2, 5, 6).

Conclusion

Early recognition of thrombotic microangiopathy and referral to reference centres is essential to optimise the outcome of patients with TMA. Every patient with TMA should receive an urgent and comprehensive work-up with Shiga toxin screening, ADAMTS13 diagnostics and exclusion of secondary forms of TMA. In this way, patients with a negative initial work-up may qualify for first-line treatment with eculizumab early in the course of the disease, which may subsequently improve the prognosis of these children.

Conflicts of interest

The authors did not receive support from any organization for the submitted work.

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