CASE REPORT

Complement factor B mutation-associated aHUS and myocardial infarction

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SUMMARY

A 6-month-old female infant was referred with a 3-day history of low-grade fever, slight nasal congestion and rhinorrhoea. On admission, the clinical findings were unremarkable and she was discharged home. However, she became progressively more listless with a decreased urine output and was once again seen in the emergency department. Analytically she was found to have metabolic acidosis, hyperkalaemia, thrombocytopenia, anaemia and schistocytes in the peripheral blood smear. Based on these findings, the diagnosis of haemolytic-uremic syndrome was made. A few hours postadmission, there was an abrupt clinical deterioration. She went into cardiorespiratory arrest and she was successfully resuscitated. An ST-segment elevation was noted on the ECG monitor and the troponin I levels were raised, suggesting myocardial infarction. Despite intensive supportive therapy, she went into refractory shock and died within 30 hours.

BACKGROUND

Atypical haemolytic uremic syndrome (aHUS) is caused by the dysregulation of the alternative complement pathway in the microvasculature and predominantly affects the kidneys. Extrarenal manifestations are observed in 20% of patients, with the myocardium and central nervous system being involved most often.¹⁻³ Acute myocardial infarction is rarely observed in the course of HUS and is associated with a poor outcome.¹⁻⁴ aHUS accounts for only 5% of all HUS cases.⁵ It characteristically affects children and young adults, with only 25% of cases occurring before the age of 6 months.⁵ A delay in the diagnosis of this entity may hinder the initiation of renal-preserving or even life-saving therapy.

CASE PRESENTATION

A 6-month-old female infant was admitted to the emergency department (ED) with a 3-day-old history of low-grade fever (maximum axillary temperature: 38.5°C), slight nasal congestion and rhinorrhoea.

On admission, she looked well and the physical examination was unremarkable. Combur test revealed a urine density of 1030, proteinuria, leucocyturia and haematuria. While on the ED she became irritable, pale and a few petechiae appeared on her legs. Her capillary refill time, heart rate and blood pressure were normal. Analytically she had a haemoglobin (Hb) 12.5 g/dL (11.3–14.1), platelets 79.000/ μ L (150.000–450.000) with platelet

aggregates on the peripheral blood smear, leucocytes 7.7 $\times 10^9$ /L (6.000–16.000), C reactive protein 0.8 mg/dL (<1), urea 9 mmol/L (1.8–6), creatinine 40 μ L (48–88) and sodium 137 mmol/L (137–147).

After a short period of observation, during which time she appeared to have recovered, she was discharged home under strict surveillance. Seven hours later she was brought again to the ED due to adynamia. On arrival, she vomited once and had a diarrhoeal stool with mucous. On physical examination, she was extremely prostrated, hypotonic and pale. Peripheral oxygen saturation was 100%, heart rate 100 bpm and blood pressure (BP) 107/70 mm Hg (P_{99}). The breath and heart sounds were normal, and she had widespread petechiae. Her mother informed that there had been no wet nappies throughout the day.

The laboratory work-up showed:

Haematology

Haemoglobin 11.9 g/dL (11.3–14.1), platelets 46.000/ μ L (150.000–450.000), leucocytes 7.850 (6.000–16.000), prothrombin time 9.4 s (10), activated partial thromboplastin time 37 s (29). Peripheral blood smear: acanthocytes and fragmented red blood cells.

Biochemistry

Urea 14.5 mmol/L (1.8–6), creatinine 75 μ mol/L (48–88) potassium 5.67 mmol/L (3.5–5.1), sodium 139 mmol/L (137–145), chloride 106 mmol/L (98–107), C reactive protein <0.5 mg/dL (<1), procalcitonin 0.96 ng/mL (<0.5), aspartate transaminase 162 IU/L (5–90), alanine transaminase 31 IU/L (5–45), creatine kinase myoglobin 30 IU/L (1–15).

Venous blood gas analysis

pH 7.31 (7.32–7.42), partial pressure of carbon dioxide 34 mm Hg (38–52), bicarbonate (HCO_3^-) 17.1 mmol/L (19–25), base excess –9.2 mmol/L

Renal ultrasound: findings compatible with acute renal dysfunction.

Based on these findings, the diagnosis of HUS was considered. Further blood samples were taken for ADAMTS13 activity evaluation and complement factors testing and she was admitted to the intensive care unit where she began supportive treatment, including plasma transfusions (20 mL/kg 8/8 hour). The blood gas analysis at admission showed: pH 7.28, K^+ 4.9 mmol/L, HCO_3^- 15.4 mmol/L and base

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excess –11.8 mmol/L. After correction of the metabolic acidosis, she remained clinically stable for 6 hours, with a mean BP of 70 mm Hg and a positive fluid balance of +230 mL without evident clinical signs of fluid overload or electrolyte disturbances.

Suddenly, there was an abrupt clinical deterioration and she went into cardiorespiratory arrest. She was successfully resuscitated and inotropic support was initiated. An ST-segment elevation was noted on the ECG monitor, suggesting myocardial infarction. The troponin I levels were 187 ng/mL (<0.034) and severe contractile dysfunction was documented on the transthoracic echocardiogram. A repeat blood gas analysis showed: pH 6.8, K^+ 6 mmol/L and lactate 15 mmol/L.

As she remained anuric and with increasing fluid overload, central venous lines were obtained for continuous renal replacement therapies, and venovenous continuous haemodiafiltration was started.

Despite progressive inotropic support (high-dose dopamine, epinephrine and norepinephrine), as well as plasma and red blood cell transfusions (minimum Hb 8 g/dL), refractory shock persisted and the platelet count dropped to 16,000 μ L/L (150,000–450,000). Twenty-four hours after admission, she had seizures with progressive neurological deterioration and clinical signs of brain stem death.

At this phase, a conjoint decision was made with the parents to limit care. She died within 30 hours of admission.

Regarding the family history, her middle brother had intrauterine growth restriction due to placental thrombosis. He died at the age of 23 days due to early-onset neonatal sepsis, anuric renal failure and cardiorespiratory arrest. The autopsy revealed haemorrhagic alveolitis and extensive alveolar damage, including parenchymal microthromboembolism. The parents and older brother are healthy. Familial thromboembolic disorders were excluded.

INVESTIGATIONS

The activity of ADAMTS13, C4 and CH50 were normal and C3 was slightly diminished:

CH50: 54 U/mL (37–57.6)

C3: 0887 g/L (0.9–1.8)

C4: 0187 g/L (0.1–0.4)

ADAMTS 13 inhibitor: 14 U Bethesda (<15)

ADAMTS 13 activity: 110% (40–130)

NTproBNP: 293,000 pg/mL (<1800)

Microbiology

Blood, urine and stool cultures: negative.

Detection of Shiga toxin-producing *Escherichia coli* in the stools was ordered, but we failed to obtain a stool sample or a rectal swab.

TREATMENT

The rapid and fulminant clinical progression in this case precluded the consideration of other treatment options, such as eculizumab.

OUTCOME AND FOLLOW-UP

The most significant lesions in the autopsy were found both in the kidneys and the heart. Kidneys: thrombotic microangiopathy lesions. Heart: microthrombi in the arterioles of the myocardium with multiple microscopic infarction lesions, especially in the anterior and posterior walls of the left ventricle (eosinophilia of muscle cells without infiltration by inflammatory cells,

suggesting recent myocardial necrosis). There were no lesions in the coronary arteries.

A skin biopsy was performed to extract DNA for genetic testing. MMACHC mutation (methylmalonic aciduria cobalamin C type, with homocystinuria) was tested and cobalamin deficiency was excluded. Mutations for complement factors CD46 (MCP), CFI, C3, THBD, CFH, CFHR1-5 and DGKE were negative.

A heterozygous mutation was identified in the exon 12 of the complement factor B (CFB), which changes a lysine at amino acid position 533 to an arginine (p.Lys533Arg). Due to ethical and legal issues, no genetic testing was performed in the parents or the brother.

DISCUSSION

aHUS is a thrombotic microangiopathy that results from uncontrolled activation of the alternative complement pathway in the microvasculature. Although aHUS typically affects the renal vessels, the same thrombotic microangiopathy phenomena may affect other organ systems, accounting for the extrarenal manifestations observed in approximately one-fifth of patients.^{1–3} Even though aHUS is classically a disease of the microvasculature, there have been descriptions of ‘macrovascular’ involvement.² Myocardial infarction has been reported in up to 3% of patients with aHUS, potentially contributing to the high mortality rates observed in these individuals.^{1,4} Postmortem studies suggest that myocardial ischaemia is a result of extensive myocardial microthrombi and/or thrombotic microangiopathy of the coronary arteries.^{4,6} Notwithstanding, clinically apparent myocardial ischaemia is a rare finding^{3,7} and may be accompanied by the classic symptoms and signs of low cardiac output, ECG alterations, ventricular dysfunction and elevated levels of troponin I.³ It could be hypothesised that the sudden collapse in the case presented may have been caused by hyperkalaemia. However, the initial blood gas analysis showed a potassium level of 4.9 mmol/L before correction of the metabolic acidosis and the ECG monitor did not show any sign suggestive of hyperkalaemia. Additionally, the patient did not present with significant fluid overload or with arterial hypertension. Therefore, the sudden onset of the ST-segment elevation and cardiorespiratory arrest suggest that the myocardial infarction resulted from an underlying condition with a specific pathophysiology and not a progressive deterioration due to other coexisting factors. In fact, the autopsy showed multiple microscopic infarction lesions throughout the whole myocardium, especially in the anterior and posterior walls of the left ventricle, further supporting this hypothesis.

aHUS is associated with a poor prognosis and elevated mortality rates, regardless of the intensive treatment regimens and life support measures.¹ More than half of patients either die from the disease, require renal replacement therapy or develop permanent kidney injury.^{1,7,8} Nonetheless, myocardial dysfunction associated with aHUS should be given special consideration since early recognition and adequate management might change the course of the disease.⁹

Genetic abnormalities are found in approximately 60% of patients with aHUS^{10–12} and include both familial and sporadic forms. These mutations or polymorphisms either increase the function of complement activator proteins or decrease the activity of regulating proteins.^{1,2} In both situations, activation of the complement system is not appropriately regulated, resulting in endothelial cell damage, platelet activation, and thrombus formation.^{1,11} These events account for the triad of mechanical

haemolytic anaemia thrombocytopaenia and kidney function impairment shared by all thrombotic microangiopathies.

The majority of patients in whom a genetic abnormality is identified carry a heterozygous mutation. Given its variable penetrance and the multifactorial nature of the disease, only 20% to 30% of patients will have a family history of aHUS.¹² Furthermore, half of the family members in whom the same mutation is identified remain healthy.¹¹ For these reasons, genetic screening is not recommended in family members of patients carrying heterozygous complement mutations.¹² On the other hand, in 35% to 40% of patients with a clinical situation compatible with aHUS, a genetic mutation will not be identified with current screening strategies.¹¹ In this case, we were not able to establish a relationship between what happened to the patient's middle brother in the neonatal period and a familial form of aHUS, since biological material was no longer available.

To the present day, mutations in six genes are known to result in increased susceptibility to aHUS: complement factor H, complement factor I, membrane cofactor protein, C3, CFB and thrombomodulin.¹²

CFB mutations account for only 1%–4% of cases of aHUS and are associated with a poor prognosis.¹³ So far, there are three known mutations in CFB associated with aHUS. In our patient, we identified the most recently described mutation in CFB¹⁴—a single nucleotide polymorphism affecting exon 12, with replacement of a lysine at amino acid position 533 by an arginine (p.Lys533Arg). As in the other mutations of CFB, this is a rare gain-of-function mutation that either leads to an increased formation of C3 convertase or to an enhanced resistance to its inactivation by complement regulators.¹⁴

Since decreased C3 levels are found in only 30% to 40% of patients with aHUS, a normal plasma concentration does not exclude the diagnosis. Moreover, a normal C4 level in the presence of a decreased C3 concentration, as was found in this case, suggests activation of the complement alternative pathway.¹²

In addition to genetic predisposition, the onset of aHUS is triggered by environmental factors such as fever, upper respiratory tract infection and diarrhoea,^{11 12} as was seen in this case. Retrospectively, in the absence of new stool samples, a rectal

swab should have been performed to exclude Shiga toxin-producing *E. coli* infection.

Ecuzumab is a humanised monoclonal antibody against complement factor C5 that works by blocking the terminal complement cascade. It has been proposed by a recent international consensus report as a first-line early treatment in children with aHUS¹² and has been associated with complete recovery of cardiac, neurological and renal dysfunction.^{10 15} In the case presented, the sudden and rapid clinical deterioration prevented us from considering its use.

Familial aHUS is associated with a worse prognosis⁸ and the early use of ecuzumab is recommended in patients with high suspicion of aHUS.¹⁵ In the case presented above, a report has been issued stating that ecuzumab should be given as early as possible to any member of this family with symptoms or signs suggestive of aHUS.

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Learning points

- Atypical haemolytic uremic syndrome (aHUS) is associated with a poor prognosis and elevated mortality rates.
- Even though aHUS typically affects the renal vessels, it may also have extrarenal manifestations that healthcare professionals should be aware of.
- Acute myocardial infarction is rarely observed in the course of HUS and is associated with a poor outcome.
- Early recognition and adequate management of aHUS with ecuzumab might change the course of the disease, with complete reversibility of the cardiac, neurological and renal dysfunction.
- Despite being rare, extrarenal manifestations of aHUS, particularly acute myocardial infarction, can be serious and rapidly fatal. A high index of suspicion is necessary, as it is possible to offer a directed and effective treatment—ecuzumab.

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