CASE REPORT

Atypical presentation of atypical haemolytic uraemic syndrome

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SUMMARY

A 17-year-old girl presented with fever, myalgia, vomiting for 1 month and oliguria and dyspnoea for 4 days. She was tachycardic, hypertensive, with pedal oedema and decreased breath sounds. She had high serum creatinine (3 mg/dL), anaemia, thrombocytopenia, leucocytosis and eosinophilia with schistocytes. Lactate dehydrogenase, transaminases were high, with low haptoglobin and high ferritin (5269 ng/mL). Complement C3/C4 and fibrinogen were normal. Urinalysis showed large blood and protein and stool studies were negative. Her ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) was normal. Kidney biopsy showed acute interstitial nephritis (AIN) in addition to thrombotic angiopathy. The differentials - haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenia (TTP) and haemophagocytic lymphohistiocytosis (HLH) were ruled out. Her genetic testing was abnormal for large CFHR1-CFHR3 homozygous deletion and heterozygous missense variant in exon 2 of *DGKE* making the diagnosis of atypical HUS. She received eculizumab and was discharged on oral steroids for AIN and biweekly eculizumab infusions with excellent recovery.

BACKGROUND

We report a case of unusual presentation of atypical haemolytic uraemic syndrome (aHUS) associated with multiple genetic mutations responsible for complement dysregulation, serositis, eosinophilia, interstitial dermatitis and nephritis, with very high ferritin and clinical resolution after administration of eculizumab. Association of laboratory findings consistent with aHUS with very high ferritin made the differentials of thrombotic microangiopathies (TMAs) broad, like TTP (which was unsupported by normal ADAMTS13 and HLH (which was ruled out by absence of other supporting data).

CASE PRESENTATION

A 17-year-old obese African-American girl with no significant medical or family history presented with decreased urine output and dyspnoea for 4 days and with history of fever, myalgia, rash, vomiting and diarrhoea for 1 month. She was tachycardic, hypertensive, with pedal oedema and had decreased breath sounds at right lung base with evidence of pleural and pericardial effusions.

INVESTIGATIONS

High serum creatinine (SCr=3 mg/dL), anaemia (haemoglobin 5 g/dL), thrombocytopenia (platelets

14.x10⁹/l), leucocytosis and eosinophilia (10%), with presence of schistocytes. She had elevated lactate dehydrogenase (LDH) and C reactive protein, low haptoglobin and high ferritin (5269 ng/mL). Her serum albumin was low with elevated transaminases and triglycerides. Her rheumatological serum markers were negative with normal complements C3/C4 and fibrinogen. Urinalysis showed large blood and protein, 4RBC, 17WBC/hpf and stool studies were negative including that of Shiga toxin. The ADAMTS13 activity was 56%, and renal biopsy showed evidence for both acute and chronic TMA and mild acute interstitial nephritis (AIN) (figures 1 and 2).

She received aculizumab with improvement of renal functions (SCr=1.1 mg/dL). Her genetic testing was abnormal for: (1) large CRHR1-CFHR3 homozygous deletion (factor H autoantibody test was negative); (2) Silent variant (c.315A>T, p.Thr105Thr) of unknown significance in exon 2 of Complement FactorI; (3) heterozygous silent variant (c.3753C>A, p.Pro1251Pro) of unknown significance in exon 29 of C3; (4) heterozygous missense variant (c.59G>A, p.Gly20Glu) in exon 2 of *DGKE*; (5) heterozygous polymorphism (IVS9-78G>A) within an intron in Membrane Cofactor Protein/CD46.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of microangiopathic haemolytic anaemia, thrombocytopenia and uraemia with elevation of acute-phase reactants includes: HUS, TTP, HLH and malignancies.¹ HUS is not an uncommon cause of acute renal failure in children with majority of cases associated with Shiga toxin-producing *Escherichia coli* (STEC). However, 10% of HUS cases are not associated with Shiga-like toxin, but may be associated with streptococcal infection, cobalamin deficiency or rarely complement deregulation—designated as aHUS.^{1,2}

Since not all HUS cases respond to treatment, it is important to find its underlying aetiology. STEC could be identified by stool or rectal swab cultures, *Streptococcus pneumoniae* by blood cultures, influenza A by PCR of nasopharyngeal swab and cobalamin C defect-associated HUS by high serum homocysteine and low methionine levels with good accuracy.¹

Acquired TTP is a rare life-threatening blood disorder causing small thrombi (clots) to form in the blood vessels. TTP results from severely reduced levels (<10%) of ADAMTS13, an enzyme (protein) that helps to break down von Willebrand factor.

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Figure 1 The biopsy shows histopathological features of both acute thrombotic microangiopathy and acute interstitial nephritis. Segmental dilation of tufts with fibrin thrombi in lumina (black arrow). Some tubules show attenuation of tubular epithelial cells and loss of brush borders (Jones methylene silver stain).

Although our patient had anaemia, thrombocytopenia-elevated transaminases and LDH, TTP was ruled out by the absence of neurological signs and normal ADAMTS13 (56%) activity.

HLH was considered in the differential because of anaemia and thrombocytopenia, high acute-phase reactants including very high ferritin (5269 ng/mL) and elevated transaminases but was unsupported by absence of splenomegaly, rash and lack of systemic infection, immunodeficiency or underlying malignancy. However, our patient had serositis/eosinophilia, along with skin rash and muscle pains (negative muscle biopsy but interstitial dermatitis in skin biopsy). Kidney biopsy had features of acute AIN in addition to TMA. We speculate that those ‘allergic’ symptoms were related to aHUS-induced immune modulation, as they clinically subsided shortly after eculizumab treatment.

TREATMENT AND DISCUSSION

Since aHUS was thought to be the most likely diagnosis, C3, C4, Complement factor H, (CFH) Complement factor 1, Complement factor B and Complement factor H antibodies along with screening for mutations for CFB, C3 and DGKE by direct

Figure 2 Electron microscopic study showed segmental duplication of glomerular basement membranes (white arrowhead) without overt immune-type electron dense deposits. Immunofluorescence study was negative for immune deposits (not shown).

sequencing analysis were requested. It should be noted that normal C3, C4, CFH and CF1 plasma levels do not exclude the diagnosis of complement-dependent HUS as only 50%–70% of complement abnormality is seen in aHUS.^{1–3} Anti-CFH antibody testing should be performed in all suspected patients with aHUS in the acute phase and before plasma exchange, which was negative for our patient.

Genetic testing should be done in all patients after confirmation that there is no STEC infection, severe ADAMTS13 deficiency, cobalamin C defect or other causes for TMA.¹ It is necessary to confirm that the disease is complement dependent to establish duration of treatment, prognosis of progression to end-stage renal disease (ESRD) and for genetic counselling.¹²

Before eculizumab became available, treatment options were limited to plasma exchanges/plasma infusions.¹ Many case reports have shown that early plasma therapy in children with CFH mutations normalised the renal function and prevented relapse for up to 6 years. However, plasma therapy only gave partial remission in patients with aHUS with almost half of children progressing to ESRD at 3 years.¹³

Eculizumab, a monoclonal anti-C5 antibody, prevents C5 cleavage and terminal complement activation.^{1,3} Four prospective, non-randomised, international trials have shown the efficacy of eculizumab with complete thrombotic microangiopathic event response with improved renal function at 26 weeks of treatment.¹³

For children with clinical diagnosis of aHUS, eculizumab is the first-line treatment to be started within 48 hours of diagnosis.¹³ The recommended dose for our patient was 900 mg weekly for four doses as induction, followed by 1.2 g at week 5 and then 1.2 g every 2 weeks lifelong. Quadrivalent meningococcal conjugate vaccination should be given before starting eculizumab therapy.¹³ If a patient has been started on plasma exchange, switching to eculizumab is recommended once the diagnosis of aHUS has been established, with the exception if the patient has anti-CFH antibodies, as plasmapheresis has been shown beneficial in those cases.¹

DGKE gene variants have recently been associated with membranoproliferative-like glomerular microangiopathy.⁴ In aHUS, pathogenic genetic variants of DGKE are usually homozygous or compound heterozygous, and the onset of aHUS is typically in the first years of life.⁵ However, there are reports of intronic DGKE mutation (c.888+40A>G) that segregated with disease.⁶ In addition, patients with DGKE mutation may not respond to eculizumab.⁵ Thus, our patient’s heterozygous missense variant in exon 2 of DGKE, found more commonly in Africans, has unclear relationship to aHUS.

CFHR1-CFHR3 homozygous deletion may be present in 5%–15% of the general population, and even as high as 33% in some populations of African descent,⁷ and has been associated with pathogenic CFH autoantibodies. Our patient was tested negative for anti-CFH antibodies, although they are found in 4%–14% of patients with aHUS (and 25% of a paediatric-only cohort). However, presence of multiple genetic mutations that have been associated with aHUS combined with clinical phenotype and response to eculizumab make our case particularly interesting.

OUTCOME AND FOLLOW-UP

We are fortunate to have long-term follow-up on our patient as she is receiving biweekly eculizumab infusions at our centre since her initial presentation with renal failure, severe haemolytic anaemia and serositis. She required plasmapheresis and

haemodialysis for 2 weeks with peak SCr=5.7 mg/dL, and urine protein:creatinine ratio (UPC) of 8.11 g/g. After eculizumab was started, her renal function improved and remained normal (SCr ranging from 0.92 to 0.61 mg/dL, with serum cystatin C=0.8 mg/L when last checked). She had no significant proteinuria 5 months of post-treatment (UPC <0.21 g/g). The soluble membrane attack complex (C5b-9) normalised from 0.36 mg/L to 0.18 mg/L in a few weeks and remains <0.3 mg/L since then

Patient's perspective

The patient said at follow-up: "I was very scared about my life at the hospital and am happy that it resolved."

Learning points

- ▶ Haemolytic uraemic syndrome (HUS) is not an uncommon cause of acute renal failure in children.
- ▶ *Escherichia coli* 0157 is the cause of HUS in the majority of cases with *Streptococcus pneumoniae*, cobalamin C deficiency and influenza in few of the cases.
- ▶ Atypical HUS (aHUS) is a disorder of dysregulation of terminal complement cascade.
- ▶ Eculizumab, a monoclonal anti-C5 antibody that prevents C5 cleavage and terminal complement activation, is the treatment of choice for aHUS.

(14 months since presentation). This phenotype-genotype correlation is highly clinically significant and offers practitioners a long-term view on aHUS disease process.

Contributors RB and RW have been involved in treating the patient and in planning, conducting, reporting, conception and design, acquisition of data, and analysis and interpretation of data. XW and CK were involved in planning, conducting, reporting, conception and design, acquisition of data, and analysis and interpretation of data.

Competing interests None declared.

Patient consent Guardian consent obtained.

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