CASE REPORT

A complementary component to atypical haemolytic uraemic syndrome

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SUMMARY

We describe a case of a 22-year-old man who presented with clinical features of atypical haemolytic uraemic syndrome and in whom genetic analysis of complement regulatory proteins demonstrated a CD46 mutation. He was treated with plasma exchange, intermittent haemodialysis and blood transfusions. At 6-month follow-up his haematological parameters and renal function showed complete resolution, and he experienced no further disease recurrence in the subsequent year.

BACKGROUND

Atypical haemolytic uraemic syndrome (HUS) is a rare disease characterised by a triad of renal failure, thrombocytopenia and microangiopathic haemolytic anaemia. More than half of patients develop end-stage renal failure and require renal replacement therapy.

Atypical HUS results from uncontrolled activity of the alternative complement pathway. Genetic studies have shown that some patients possess mutations in one or more complement regulatory proteins.

These advancements have led to the use of novel therapies, such as Eculizumab (a humanised monoclonal antibody directed against complement factor C5) to treat acute exacerbations as well as prevent post-transplant recurrences and improve long-term renal function.

Patients with atypical HUS should be considered for genetic testing of complement factors to aid clinical management.

CASE PRESENTATION

A 22-year-old Caucasian man presented with a 3-day history of fever, abdominal pain and dark urine. He denied any diarrhoea, bloody/pale stools or flu-like symptoms. His medical history included psoriasis. Physical examination was unremarkable. His blood pressure was 150/84 mm Hg, pulse rate 90 bpm and temperature 36.7°C.

INVESTIGATIONS

Urinalysis revealed proteinuria and microscopic haematuria. Baseline blood tests showed haemoglobin 11.4 g/L (range 13.3–17), platelets 20×10^9 /L (range $140\text{--}400 \times 10^9$ /L), urea 19.3 mmol/L (range 2.1–7.1) and creatinine 443 μ mol/L (range 66–112). A blood film demonstrated schistocytes. Stool cultures ($\times 3$) were negative for *Escherichia coli* 0157: H7 strains and *Shigella* species. Ultrasonography showed normal kidneys with no evidence of

obstruction, calcification or calculi. Immunological studies for antinuclear, antidouble-stranded DNA, antiglomerular basement and antineutrophil cytoplasmic antibodies were all negative. Complement C3 56 mg/dL (range 70–165) and C4 4 mg/dL (range 16–54) were low, ADAMTS13 activity was within normal range, and serology for HIV and viral hepatitis B/C were negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for atypical HUS include typical HUS (caused by Shiga toxin-producing *E coli*) and thrombotic thrombocytopenic purpura (TTP; resulting from a deficiency of von Willebrand cleaving protease ADAMTS13). These diseases are both characterised by microvascular thrombosis, leading to thrombocytopenia, haemolytic anaemia and renal or neurological dysfunction.

TREATMENT

Our patient was initially treated for suspected TTP with both intravenous methylprednisolone and immunoglobulin. Despite this, repeat blood tests on day 3 of admission showed haemoglobin 6.7 g/L, platelets 10×10^9 /L, urea 37 mg/dL and creatinine 703 μ mol/L. His lactate dehydrogenase (LDH) was 1784 IU/L (range 240–480), haptoglobins 3 g/L (range 0.3–1.99) and clotting screen remained unremarkable. Further treatment then included plasma exchange, blood transfusions and intermittent haemodialysis.

Genetic testing for mutations within the regulatory complement proteins: complement factor H, complement factor I and CD46 (also called membrane cofactor protein) demonstrated a heterozygous missense mutation in exon 2 of CD46 c.175C>T; p. Arg59Stop (figure 1). A diagnosis of atypical HUS with a CD46 mutation was therefore made.

OUTCOME AND FOLLOW-UP

Over the subsequent fortnight his serum creatinine, platelet count, LDH and haemoglobin level normalised and at 6-month follow-up showed complete resolution. He experienced no further disease recurrence in the subsequent year.

DISCUSSION

A triad of acute kidney injury, thrombocytopenia and microangiopathic haemolytic anaemia, without evidence of Shiga toxin-producing bacteria and normal ADAMTS13 activity, suggests a diagnosis of atypical HUS.

Atypical HUS is a rare disorder associated with mutations in complement genes encoding proteins

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Figure 1 Genetic analysis—DNA sequencing electropherograms demonstrating a healthy control individual and the heterozygous c.175C>T mutation in exon 2 of *CD46*. Normal control and patient DNA sequences and corresponding nucleotides are shown. The missense mutation (indicated with an arrow) changes the amino acid from arginine (CGA) to a stop codon (TGA).

Figure 2 Pathogenesis of atypical haemolytic uraemic syndrome (HUS) – Mutations of complement regulators factor H, factor I and CD46 lead to excessive activation of the alternative complement pathway. This generates cytoactive molecules (C3a, C3b, C5a) and the membrane attack complex (MAC), which cause renal parenchymal and vascular endothelial cell injury. Cell damage results in increased platelet adherence and the formation of microthrombi in the kidney, thus explaining the characteristic triad of atypical HUS: acute renal failure, thrombocytopenia and haemolytic anaemia.

involved in regulation and activation of the alternative complement pathway. It may be genetic, acquired or idiopathic.¹ The pathogenesis is believed to involve 'loss-of-function' mutations encoding complement regulators (factor H, factor I, CD46) and/or 'gain-of-function' mutations in complement activators (C3, factor B), leading to unopposed activation of complement, endothelial cell damage and thrombosis in the microvasculature of the kidney² (figure 2).

CD46 is a widely expressed transmembrane complement regulator that protects host cells against complement-mediated damage.³ CD46 mutations result in either failure of expression of the regulatory protein or an expressed mutant protein that has impaired complement regulatory function. To date, over 40 different CD46 mutations have been identified in patients with atypical HUS. In our patient, mutation screening identified a missense CD46 mutation that resulted in a premature stop codon and thus failure of expression (figure 1).

Empirical treatment with plasma exchange is recommended for patients with atypical HUS. The majority of patients with a CD46 mutation will recover renal function, but may have recurrent episodes of atypical HUS. It is important to note that because CD46 is not a circulating plasma protein, plasma exchange has a limited role in treatment and most patients achieve remission without it.²

Overall atypical HUS has a poor prognosis. Within 3 years of presentation 30–60% of patients develop end-stage renal failure and require renal replacement therapy. In addition, following renal transplantation up to half of all patients may develop disease recurrence and up to 90% may develop graft loss.⁴ The prognosis of atypical HUS varies according to the underlying complement mutation. In patients with a CD46 mutation, post-transplant recurrence is low because the renal allograft has a normal CD46. In contrast, there is a very high risk of graft disease recurrence in patients with mutations affecting factor H and factor I, both of which are soluble circulating proteins produced by the liver.⁵ Combined liver–kidney transplantation has been undertaken in a small number of such patients with varying results. Interestingly, recent trials of the C5 complement inhibitor Eculizumab have demonstrated the potential to prevent post-transplant/graft recurrence and revolutionise the treatment of atypical HUS.⁴

In summary, all patients with atypical HUS should be considered for genetic testing to identify mutations in complement regulatory proteins. Identifying such abnormalities is essential to optimise clinical treatment.

Learning points

- ▶ Atypical haemolytic uraemic syndrome (HUS) is a rare disease characterised by a triad of renal failure, thrombocytopenia and microangiopathic haemolytic anaemia.
- ▶ More than half of patients develop end-stage renal failure and require renal replacement therapy.
- ▶ The underlying pathophysiology may include genetic mutations in one or more complement regulatory proteins.
- ▶ All patients with atypical HUS should be considered for genetic screening of complement factors to aid clinical management, and provide prognostic information in predicting renal recovery and transplant outcome.

Competing interests None.

Patient consent Obtained.

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