

## A rare case of cutaneous involvement in atypical haemolytic uraemic syndrome successfully treated with eculizumab

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### ABSTRACT

Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening, genetic disease, due to uncontrolled alternative pathway complement activation. Although the renal microvasculature appears to be the predominantly affected target, other organ pathology compatible with local thrombotic microangiopathy has been reported. Eculizumab is a humanized antibody therapy that has been associated with significant inhibition of complement-mediated thrombotic microangiopathy events in aHUS. In this report, we describe the rare case of a patient with relapsing atypical haemolytic uraemic syndrome, cutaneous manifestations of the thrombotic microangiopathy and we discuss the treatment with plasma exchange and eculizumab.

**Key-Words:** Atypical haemolytic uraemic syndrome; complement mutations; eculizumab.

### INTRODUCTION

Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening disease due to uncontrolled alternative pathway complement activation. This impairment leads to inappropriate complement activation on endothelial cells, platelet recruitment, and intravascular thrombus formation in renal arterioles and capillaries<sup>1-3</sup>. Eculizumab is a humanized monoclonal antibody (mAb) against complement protein C5 that inhibits the generation of the pro-inflammatory peptide C5a and the formation of the membrane complement complex C5b-9<sup>3</sup>. It has been associated with significant inhibition of complement-mediated thrombotic microangiopathy (TMA) as measured by a change in the platelet count and an absence of TMA events in aHUS patients<sup>3,4</sup>.

Here we report the effect of eculizumab in the treatment of cutaneous involvement on a aHUS patient with homozygosis complement factor H (CFH) and heterozygosis membrane cofactor protein (MCP) mutations.

### CASE REPORT

A 35-year-old female presented to our hospital with painful skin lesions. Her past medical history included: one uneventful pregnancy and a second pregnancy complicated by pre-eclampsia and C-section performed at the 29th week of gestation; chronic kidney disease (CKD) on haemodialysis due to aHUS, diagnosed after her second pregnancy.

A few months after childbirth, she presented with severe hypertension and oedema and the workup performed showed microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury possibly triggered by pregnancy or respiratory infection. Initial investigation revealed: Coombs-negative haemolytic anaemia (haemoglobin 7.5 g/dL) with red blood cell fragmentation, platelet count  $46 \times 10^6/\mu\text{L}$ , serum haptoglobin  $< 0.2$  mg/dL, serum creatinine 6.5 mg/dL, and urinalysis showed microscopic haematuria and proteinuria (4.9 g/day). The diagnosis of aHUS was established on the absence of autoantibodies against ADAMTS13. Complement analyses indicated complement alternative pathway activation. Mutation screening of *CFH*, *MCP* and *CFI* by Sanger sequencing revealed homozygosity *CFH* mutation (c.332 C > T, V62I, Y402H, H672Q, E936D – TGTGT) and heterozygosity *MCP* mutation (c.287-2 A>G, IVS2-2A>G).

She had no known family history of kidney disease or aHUS. She was started on plasma exchange (PE) and fresh plasma infusion (FPI); although the haemolysis parameters showed normalization, there was permanent kidney failure and the patient remained dialysis dependent.

During the first year after diagnosis, two aHUS recurrences occurred. The first one presented isolated haematological commitment (haemolytic anaemia and thrombocytopenia) that was resolved after 6 months of PE. The second aHUS recurrence occurred 4 months after PE/FPI withdrawal and the patient started complaining of three painful leg skin lesions that progressed to ulcers, with some necrotic areas on the base and edges, described elsewhere<sup>4</sup>. Immunologic studies including antiphospholipid antibodies remained normal. A skin biopsy showed fibrin thrombi in the small blood vessels compatible with thrombotic microangiopathies (TMA), with discrete inflammatory infiltrate of lymphocytes and plasma cells. One month after the appearance of the skin lesions the patient developed thrombocytopenia. The beginning of PE/FPI led to the resolution of haematological and cutaneous disorders and was maintained for another 6 months.

Five months after stopping PE, the patient had another cutaneous relapse. At this time, the investigation revealed: haemoglobin 8.9 g/dL with red blood cell fragmentation, platelet count  $143 \times 10^6/\mu\text{L}$ . She promptly initiated PE/FPI. After 3 months of PE/FPI the haematological parameters normalized but with only partial improvement of the skin lesions. Eculizumab

was initiated and no additional PE treatment was done after the initiation of eculizumab. The cutaneous ulcer was completely healed and there was a reduction in the need for erythropoietin and for antihypertensive drugs. She received prophylactic antibiotic (ciprofloxacin 250mg bid) until 2 weeks after immunization for meningococcal infection. The patient received eculizumab 900 mg weekly for one month followed by 1200 mg every two weeks for 11 months. She had no signs of recurrence of haematological or dermatological lesions and no reported adverse effects. At this time, eleven months after stopping therapy she shows no signs of recurrence.

## ■ DISCUSSION

Extra-renal TMA manifestations are observed in up to 20% of patients, including involvement of the central nervous system, cardiovascular system, lungs, skin, skeletal muscle, and gastrointestinal tract. As previously reviewed those extra-renal complications may not only be observed during the disease's acute phase but can also manifest to some degree years later and are thought to result from a chronic over activation/dysregulation of the complement system<sup>6</sup>. Affected patients have a lifelong risk of systemic clinical complications of TMA.

In the patient reported here, we noted perfusion defects of arterioles supplying the skin, leading to gangrenous and ulcer lesions that appeared before the haemolysis parameters. Gangrenous lesions of the finger and toes were reported in six children with aHUS in three case reports [7-9]. Ardiassino *et al.* describe three cases of complement-mediated aHUS, two with a *CFH* mutation and one with antibody against *CFH*, who developed skin lesions that completely recovered after PE or eculizumab. Only one patient underwent skin biopsy and histological findings were compatible with TMA. None of the patients showed laboratory signs of aHUS activity<sup>10</sup>.

The presence of genetic abnormalities in circulating complement proteins in many patients with aHUS provides a rationale for FPI to correct the complement regulatory dysfunction. However, several patients do not respond to PE/FPI or require long-term treatment in this relapsing disease<sup>3,11</sup>. In our patient, PE/FPI failed to prevent progressive renal failure and ongoing aHUS activity manifested as acute flare-up with cutaneous involvement. Treatment with eculizumab prevents C5b formation and consequently the haemolysis-dependent of the

endothelial aggression<sup>2-4,6</sup>. The present patient displayed reduction in intravascular haemolysis due to eculizumab that was maintained for 12 months. As previously reported, eculizumab was used to treat catastrophic extrarenal complication like peripheral gangrene unresponsive to PE in a child<sup>8</sup> and cutaneous manifestation in adults<sup>9</sup>. Some authors showed that earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. These results suggest that starting eculizumab treatment earlier may lead to improved clinical outcomes and reversal of organ damage<sup>4,11</sup>. Early administration of eculizumab could have decreased the extent of irreversible renal damage in our patient, but the drug was unavailable at that time. Complement-targeting therapy with eculizumab is a valuable add-on or alternative to plasma therapy, but efficacy seems to vary; the determinants of treatment response are still unknown and the optimal duration of treatment remains to be determined.

In conclusion, 12 months of eculizumab treatment in a patient with a previously PE-dependent aHUS was safe and effective in controlling the TMA and haemolysis without the associated use of PE/FPI. This case report highlights that aHUS is a systemic disease and that targeting the complement system may modify disease progression and treat aHUS more effectively.

**Disclosure of potential conflicts of interest:** None declared

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