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ECULIZUMAB TREATMENT IN DE NOVO ATYPICAL HAEMOLYTIC URAEMIC SYNDROME AFTER RENAL TRANSPLANTATION ASSOCIATED WITH COMPLETE DEFICIENCY OF FACTOR-H RELATED PROTEINS 1 AND 3

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OBJECTIVES

The incidence of *de novo* thrombotic microangiopathies (TMA) vary between 1-14 %. Typically *de novo* TMA develops in the early posttrasplant period, but it may also 2-6 years after transplantation. Risk factors includes ischemia-reperfusión injury, acute rejection, viral infections and calcineurin inhibitors (CNIs). Abnormalities in complement regulation underlie up to 30% of patients with de novo aHUS after renal transplantation (Tx), a disease that leads to graft loss in more than one third of the cases. Complement inhibition with Eculizumab is the treatment of choice in recurrent and de novo aHUS, exceeding plasma exchange (PE) with regard to efficacy and safety.

We present a case of post-Tx aHUS associated with homozygous deficiency of the complement proteins FHR1 and FHR3, and anti-Factor H antibodies acquired following PE.

METHODS

A 18-year-old female developed aHUS two years post-Tx of her 2nd graft from a cadaveric donor (CKD origin unknown). First graft failed due to delayed active rejection C4d/DSA negative 1 year after Tx. Immunosuppression: thymoglobulin, tacrolimus, MMF, corticosteroids. Good renal function with no complications for the first year (Cr 0.9 mg/dl, GFR 98 ml/min).

18 months after Tx, Cr 2.77 mg/dl, suspected acute rejection, renal biopsy inconclusive. Following thymoglobulin, methylprednisolone, IVIG, Cr 2.5 mg/dl. 23 months post-Tx she suffers late TMA (Graph 1): Cr rose to 3.54 mg/dl, anaemia with schistocytes (Hb 6.8 g/dl), thrombocytopenia (44,000/mm3), LDH 820 U/l, proteinuria 0.95 g/dl. ADAMTS13 58%, STX 1/2, CMV, BK, antiphospholipid, ANAs, anti-DNA antibodies, DSAs by Luminex all negative.

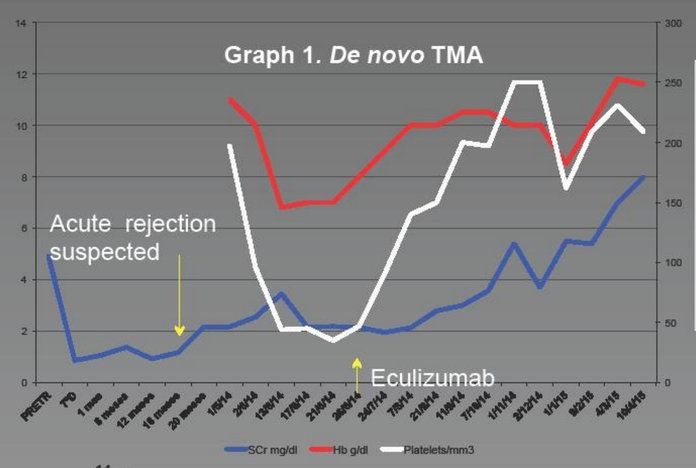
Kidney biopsy (Figure 1-3): Glomerular and arteriolar thrombotic microangiopathy (TMA) no signs of rejection, C4d and SV40 negative.

No response to suppression of tacrolimus, sCr reaches 3.45 mg/dl. Transfusion (4 IUs packed red blood cells, 1 IU platelets). Because of poor prognosis associated to late TMA and sistemic involvent, PE started on 4th day (5 sessions) with no haematologic response, Cr stabilising at 2.2 mg/dl and GFR 23 ml/min. She presented a plasma reaction and PE was stopped.

Eculizumab was started (day +14), normalising haematologic parameters and improving graft function (GFR 53 ml/min). However, worsening of graft function coinciding with fortnightly eculizumab treatment required adjustment to weekly treatment.

Genetic analysis revealed that the patient is homozygote for the CFHR3-CFHR1 deletion. No anti-FH antibodies were detected when treatment started, but were positive at the time of recurrence.

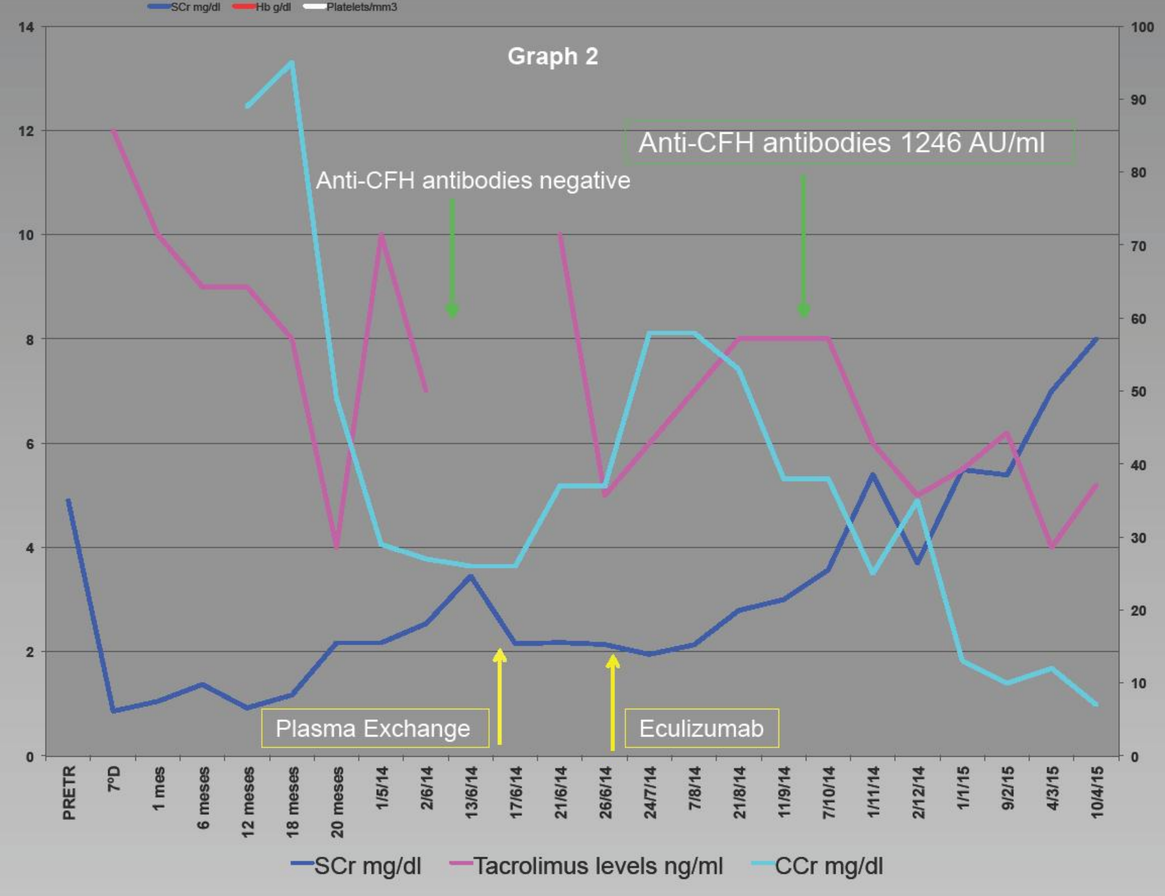
Graph 1. *De novo* TMA



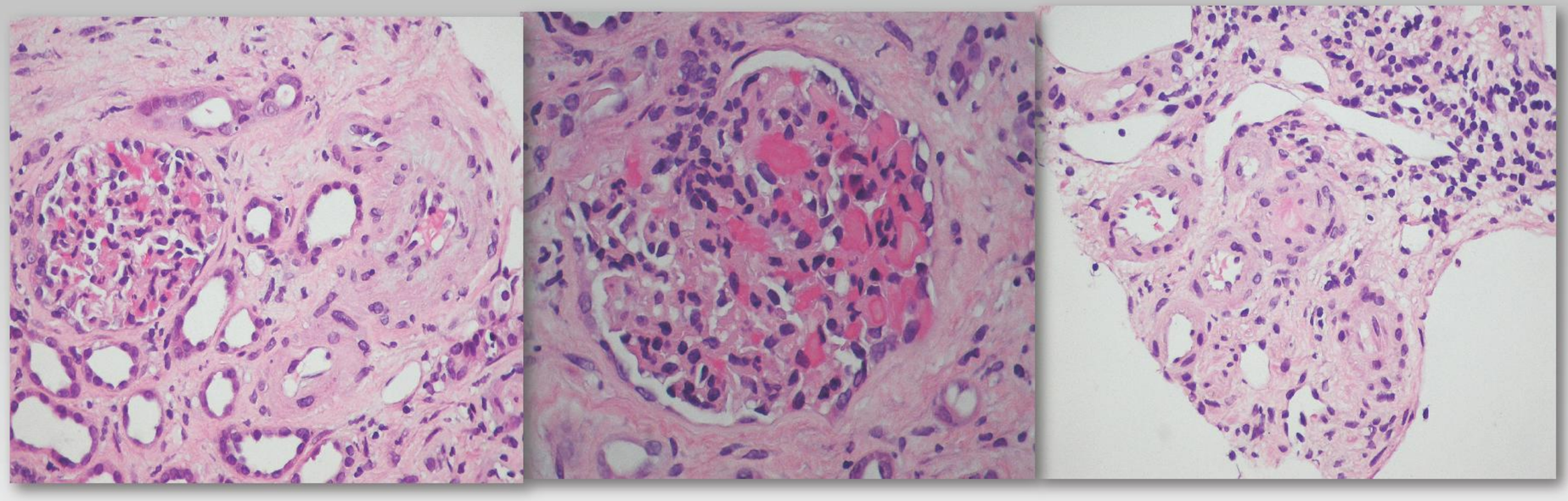
Complement Investigation

Homozygous for CFHR3/1 delection (MLPA)
Mutation c.1697A>C; p.Glu566Ala exon 13 CFB (no functional impact, Marinozzi MC, JASN 2014)
Genetic analysis negative for CFH, CFI, MCP/CD46 and CFHR5.

Graph 2



Renal transplant biopsy:
Thrombotic microangiopathy glomerular and arteriolar.
Interstitial fibrosis and tubular atrophy.
g0,mm0, cg0, i0t0
V0cv1,ah0
C4d, SV40 negative



RESULTS

- The aetiological diagnosis of de novo aHUS after renal Tx is complicated, given that it co-occurs with TMA-related factors. In our case, viral aetiology and rejection were ruled out with no clinical-histological tacrolimus toxicity data, and C4d and SV40 negative in two renal biopsies.
- Homozygous CFHR3-CFHR1 deletion in aHUS is associated with the generation of anti-FH antibodies. In our patient these anti-FH antibodies were first detected after PE, indicating a possible sensitisation to the FHR1/FHR3 infused plasma proteins (Graph 2).
- Le Quintrect et al failed to demostrate a significant relation between CNI therapy and recurrence of aHUS. At the opposite significant risk factor of recurrence was found in imTOR treated patients with HUS and withdrawing CNI treatment increases the risk of acute rejection.
- Treatment with eculizumab was initially effective in our patient to block endothelial damage by complement, improve renal function and haematological remission, although weekly treatment was required, perhaps due to the presence of anti-FH antibodies.
- Eculizumab has been successfully used in a 13-year-old female with AMR associated with complement factor H-related protein 3/1 deficiency. Nevertheless, it has failed to rescue our patient despite early treatment combined with immunosupresion, rituximab and IVIg and she lost their graft within 1 year after diagnosis of TMA.
- Differencial diagnosis between TMA-IFTA and vascular rejection may be difficult even with graf biopsy and No-HLA rejection not may be excluded as a contributory factor.

CONCLUSIONS

- Complement abnormalities underlie a significant number of patients with de novo aHUS after renal transplantation.
- Treatment with Eculizumab is the first-line treatment.
- Importantly, plasma infusions should be avoided in patients homozygous for the CFHR3-CFHR1 deletion to avoid the potential generation of anti-FH antibodies.

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