Pathogenic mutations in the alternative complement pathway in patients with Bone Marrow Transplant associated Thrombotic Microangiopathy (TA-TMA).

Pathogenic variants in the alternative complement cascade have been identified in patients presenting with atypical haemolytic uraemic syndrome (aHUS). This understanding has allowed the introduction of the complement inhibitor, eculizumab, for the treatment of aHUS. Activation of the endothelium occurs during HSCT and results in an increased susceptibility to thrombotic microangiopathy; occurring in up to 25% of cases. The role of complement dysregulation and specifically eculizumab in this cohort is unclear.

We report a 2 year old girl with a background of Artemis SCID who developed features of TA-TMA soon after bone marrow transplantation (figure 1). She was initially treated with defibrotide, with a good response. However, approximately two months after Bone Marrow Transplant (BMT) she developed an apparent relapse of her condition and was once again started on defibrotide. Despite treatment with defibrotide her renal function continued to deteriorate; in view of this we undertook a renal biopsy that confirmed active TMA; genetic analysis was undertaken to investigate her alternative complement pathway and she was converted to eculizumab. Genetic analysis revealed a likely pathogenic variant in complement factor H (c.532T>G (p.Cys178Gly)). At last follow-up, she had no signs of active TMA, although there was evidence of chronic kidney disease and was maintained on eculizumab with evidence of adequate complement blockade (absent CH50/AH50).

Following identification of this variant we performed a review of all cases of TA-TMA referred to the National Renal Complement Therapeutic Centre (n=27) and identified two further cases where genetic screening revealed pathogenic variants in aHUS-related genes (one in CD46 and one in CFH).

Conclusions

Within this select population of patients developing TA-TMA we identified genetic variants in the alternative complement pathway in 11% of cases. These results highlight the importance of genetic screening in patients who develop TA-TMA, as prompt diagnosis of complement mediated disease will enable early initiation of anti-complement therapy and aid to prevent or reduce the long-term renal morbidity in these cases.

