

Post-transplant CFHR5 mutation-related atypical HUS: The need for pre-transplant diagnosis

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy (TMA) affecting multiple organs and can be sporadic or familial. It is most commonly caused by dysregulation of the alternative complement pathway. aHUS can occur at any age with a high rate of progression to end-stage kidney disease. We describe the case of a 24-year-old man with chronic kidney disease, severe hypertension, and antineutrophilic antibody by IF positive. On biopsy, diffuse global glomerulosclerosis with TMA and IF findings of full house pattern suggestive of lupus nephritis were present. Considering a lupus nephritis case, after 2 years of hemodialysis underwent live-related renal transplant (Father Donor). Immediate post-transplant period developed severe cortical necrosis and TMA. An etiological workup was done to ascertain the cause of post-transplant TMA. After excluding common causes of antibody-mediated rejection (C4d and donor-specific alloantibody neg), calcineurin inhibitor toxicity, and infection, we detected an abnormal complement CFHR5 mutation with an autosomal dominant pattern of inheritance. Pre-transplant diagnosis could have prevented taking the kidney from the father for transplant and further prevented recurrence. Systemic lupus erythematosus and TMA both can have alternate complement pathway dysregulation leading to full house IF pattern and misdiagnosis.

Key words: Atypical hemolytic uremic syndrome, Glomerulonephritis, Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) as seen in atypical hemolytic uremic syndrome (aHUS) due to abnormal complement has a relapsing course and may result in permanent renal impairment. It is an extremely rare disease that differs from typical HUS which is usually associated with Shiga toxin-producing *Escherichia coli*. Typical HUS usually resolves with supportive care and subsides on the removal of the underlying cause [1,2].


CASE REPORT

A 24-year-old man presented with chronic kidney diseases, severe hypertension, and antineutrophilic antibody (ANA) positivity by IF study. Native kidney biopsy showed diffuse global glomerulosclerosis and full house pattern on IF study suggested the possibility of immune complex-mediated glomerulonephritis. ANA profile was advised to rule out systemic lupus erythematosus

(SLE). Slides, blocks, or images of this biopsy were not available for review. After 2 years of maintenance hemodialysis, he underwent live-related kidney transplant (Donor – Father). Anti-thymocyte globulins (ATG) induction was given.

On post-operative day 3 (POD3), serum creatinine increased from 4.4 to 5.6 mg/dL and the patient also had severe hypertension requiring three antihypertensive drugs. Tacrolimus level was 20 ng/mL. On ultrasonography, the graft renal artery showed a low RI (Refractive Index) of 0.5–0.6.

A biopsy was performed with a clinical diagnosis of acute tubular necrosis and antibody-mediated renal graft rejection. During the subsequent course, three graft renal biopsies were performed on POD 3, POD 7, and POD 14. Renal biopsy showed infarction of tubules and glomeruli with fibrin thrombi. Blood vessels show fibrointimal hyperplasia, intimal mucoid edema, and fibrinoid necrosis near completely obliterating vascular lumina. IF and C4d studies in allograft biopsies were negative. An electron microscopic (EM) study done in biopsy of POD 7 showed no evidence of TMA or immune complex-mediated disease could be confirmed (Fig. 1).

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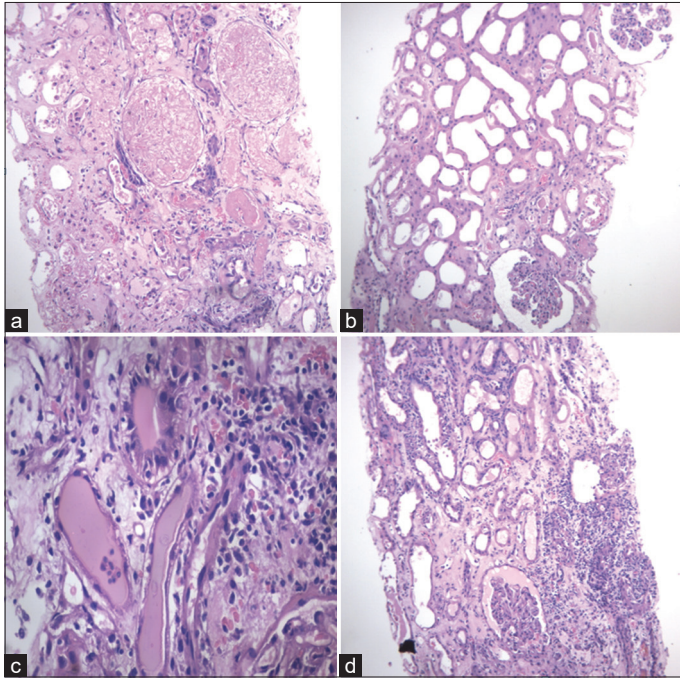


Figure 1: HE-stained section shows (a) marked cortical necrosis of glomeruli and tubules in POD3 graft biopsy; (b) Acute tubular necrosis (Viable area) POD-7; (c and d) Acute T cell-mediated rejection (Tubulitis) POD-14. POD: Post-operative day

A diagnosis of TMA was offered and clinical correlation for various etiologies was suggested. The most common causes of TMA in post-transplant patients are antibody-mediated rejection (ABMR), calcineurin inhibitor (CNI) toxicity, and infection. Workup for etiology of TMA was done as follows: (a) ABMR was ruled out as C4d and donor-specific alloantibody was negative. (b) CNI toxicity: Tacrolimus dose was reduced but due to the reduction in immunosuppression, the patient developed acute T cell-mediated rejection (as seen in the 14th POD biopsy) and biopsy changes of TMA persisted which excluded CNI toxicity but still tacrolimus was replaced by cyclosporine. There was no obvious infective etiology (bacterial, viral). A possibility of classical Shiga toxin-related hemolytic uremic syndrome was ruled out. Native kidney biopsy also had TMA and had demonstrated a full house IF pattern and pre-transplant ANA had been positive leading to concern about the possibility of recurrence of SLE in the graft biopsy. However, post-transplant ANA was negative, IF on all post-transplant biopsies was negative, and on EM, there was no evidence of immune complex glomerulonephritis.

Other etiologies that were common in native kidneys (hemolytic uremic syndrome, thrombotic thrombocytopenic [TTP]) were then considered. (a) ADAMTS 13 was done to rule out TTP - was in the normal range. (b) Antifactor H antibody was negative by enzyme-linked immunoassay, ruling out antibody against complement. (c) Mutation analysis of complement system to rule out atypical HUS. The results showed that CFHR5, exon 7 heterozygous deletion of unknown significance (VUS c.993>A (p.Cys331Ter) was found with an autosomal dominant pattern [3].

The final diagnosis offered as post-transplant recurrent CFHR5 mutation-related aHUS (familial aHUS).

DISCUSSION

aHUS is an extremely rare disease that differs from typical HUS which is usually associated with Shiga toxin-producing *E. coli*. Typical HUS usually resolves with supportive care (e.g., fluid rehydration, red cell transfusions) and subsides on removal of the underlying cause in contrast to aHUS which has a relapsing course and may result in permanent renal impairment.

As is well known, the complement system is a complex group of proteins that work together to fight infection in the body. Complement proteins respond to bacteria, viruses, or other foreign substances in the body and ultimately produce a large multi-protein complex (C3 convertase) that directly attacks these foreign invaders. Other complement proteins regulate the formation of this attack complex to protect the body's cells from being damaged. Individuals with aHUS have a mutation in one or more of the genes that encode the complement regulatory proteins [2,3].

About 30% of the time, aHUS is associated with malfunctions in the gene (CFH) responsible for the production of a blood protein known as factor H which is one of the regulatory proteins of the complement system. CFHR5 is located in the regulator of the complement activation gene cluster on chromosome 1 and is constituted by 20 short consensus repeats (SCR). The two binding sites for C3b are in SCR 1–4 and 19–20. The binding sites for polyanions of the cell surface (vascular endothelium) are in SCR 7 and 19–20. SCR 1–4 are involved in the binding of CFH to circulating C3b, that is, the regulation of complement alternative pathway activation in the fluid phase. SCR 7 and 19–20 are involved in the binding of CFH to polyanionic surface-bound C3b, that is, the regulation of complement alternative pathway activation at the endothelial cell surface as shown in Fig. 2.

Complement regulatory proteins may be impaired in their action by loss-of-function mutations (CFH, CFI, CD46, and THBD) or acquired antibodies (specifically to complement factor H). Conversely, potentiation may be augmented by gain-of-function mutations in CFB or C3. Anti-factor H autoantibodies have been reported in 6–10% of cases, mainly children. Less often, autoantibodies that target other complement proteins have been identified. In approximately 30–50% of individuals with aHUS, no mutation in a complement gene and no autoantibodies can be detected. These individuals may be referred to as having idiopathic aHUS.

CFH and CFH-related proteins regulate the alternative complement pathway by (i) competitively binding C3b to prevent C3 convertase activity and (ii) acting as a cofactor for the proteolytic inactivation of C3b by complement factor I [4-6].

The genetic mutations in complement genes that predispose individuals to aHUS usually occur sporadically, meaning that there is no previous family history of the disorder. The disorder has run in families only about 20% of the time. In such instances, these mutations are transmitted (inherited) as an autosomal dominant trait or, less often, as an autosomal recessive trait. The penetrance of the disease is low, as less than half of family members carrying the same mutation as the patient with atypical HUS will be affected by the disease. The risk is the same for

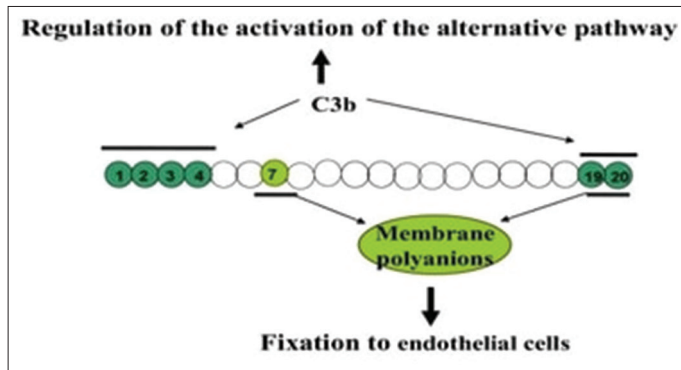


Figure 2: Structure of CFHR5 on Chromosome 1

males and females. Frequent recurrences and if untreated become chronic with severe hypertension and end-stage renal disease.

The patients with aHUS are treated with plasmapheresis and eculizumab (an expensive drug) which is a humanized immunoglobulin G2 monoclonal antibody against complement C5. Prior to the availability of eculizumab, 50% of aHUS patients relapsed after kidney transplant resulting in a graft failure rate of 80–90% after relapses. Currently, aHUS patients who undergo kidney transplants require rigorous risk assessment and preparation including vaccinations and administration of eculizumab to be started prophylactically prior to and continued after transplant. The length of prophylactic therapy with eculizumab after a kidney transplant depends on the risk of recurrence in the recipients. Patients with a high risk of recurrence (FH, C3, and FB mutations) need lifelong prophylactic eculizumab therapy [7,8].

CONCLUSION

Pre-transplant diagnosis of aHUS as an etiology of TMA with more robust genetic tests and functional complement assays, with quicker turnaround, are needed to facilitate the diagnosis and monitoring of the therapeutic response of aHUS patients. Living donor transplants (particularly from members of the same family)

are contraindicated in aHUS patients due to concerns about the possibility of recurrence of aHUS in the transplanted kidney. Full house pattern on IF study with ANA positive by IF needs confirmation by ANA profile study for the diagnosis of SLE.

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