Atypical Hemolytic Uremic Syndrome Recurrence after Renal Transplantation
C3-Glomerulonephritis as an Initial Presentation

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Abstract: Risk for atypical hemolytic uremic syndrome (aHUS) recurrence after renal transplantation is low with an isolated membrane cofactor protein mutation (MCP). We report the case of a 32-year-old woman with a MCP who underwent kidney transplantation with a good evolution at 12 months. At 15 and 35 months, 2 episodes of thrombotic microangiopathy (TMA), after a miscarriage and a preeclampsia, were misinterpreted as triggered by tacrolimus. After each episode however serum creatinine returned to baseline. Five years after transplantation, she had a self-limited rhinosinusitis followed 3 weeks later by an oliguric renal failure. Her complement profile was normal. Graft biopsy showed C3 glomerulopathy with no "humps" on electron microscopy. No significant renal function improvement followed methylprednisolone pulsing. A second biopsy showed severe acute TMA lesions with C3 glomerular deposits. Despite weekly eculizumab for 1 month, dialysis was resumed. A new workup identified the "at-risk" complement factor H haplotype. Thus, aHUS recurrence should be ruled out in aHUS patients considered at low recurrence risk when a TMA is found in graft biopsy. Prompt eculizumab therapy should be considered to avoid graft loss as aHUS recurrence can first present as a C3 glomerulonephritis.

Received 1 December 2014. Revision requested 5 February 2015. Accepted 24 February 2015.

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The authors declare no funding or conflicts of interest.

Y.B. drafted the manuscript. V.F.B. performed the genotyping and provided her expertise in the field through a review of the manuscript. J.V. took part to the case management on the immunological point of view. S.M. reviewed the kidney biopsies and provided the biopsy pictures. P.-Y.M. participated in the writing of the paper. K.H. managed the case as well as thoughtfully revised the manuscript.

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ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000000518

(Transplantation Direct 2015;1:e9; doi: 10.1097/TXD.0000000000000518. Published online 26 March 2015.)
MCP mutation and an “at risk” complement factor H (CFH) haplotype.

**CASE REPORT**

A 24-year-old white woman presented with an initial episode of epigastralgia, lower limb edema, hypertension, acute kidney injury, and hemolytic anemia leading to aHUS diagnosis triggered by herpes infection. She presented 2 subsequent episodes of aHUS treated with plasma exchanges. Kidney biopsies showed severe arteriolar wall thickening with glomerular ischemia, thickening of the glomerular capillary wall with double contours, 2 lesions of focal and segmental glomerulosclerosis (FSGS), and diffuse interstitial fibrosis. The latter episode led the patient to peritoneal dialysis.

During her workup for kidney transplantation, ADAMTS13 abnormalities were ruled out, and serum antiphospholipid, antinuclear, and antinucleosome antibody assays were negative. The complement profile (CH50, 118%; C3, 0.72 g/L; and C4, 0.24 g/L) was within the normal range (namely, CH50, 75%-125%; C3, 0.57-1.16 g/L; and C4, 0.11-0.28 g/L). An MCP mutation was identified: 218 C > T (R25Stop). At 32 years of age (2007), the patient underwent a deceased kidney transplantation. The immunosuppressive regimen consisted of basiliximab, methylprednisolone, tacrolimus, and mycophenolate mofetil. Her serum creatinine was 68 μmol/L on day 7. One-year protocol biopsy was normal, and serum creatinine was 94 μmol/L allowing corticosteroids tapering.

At 15 months after transplantation, mycophenolate mofetil was switched to azathioprine because the patient wanted to get pregnant. After a first-trimester miscarriage, a 50% increase in serum creatinine was explained by a biopsy-proven diffuse T cell–mediated rejection Banff IB and treated with methylprednisolone pulses and polyclonal antibodies (thymoglobulin, 1.5 mg/kg per day for 7 days). A month later, serum creatinine did not return to baseline. Tacrolimus toxicity was suspected based on a new graft biopsy with acute TMA lesions. Lower trough concentration was targeted. Serum creatinine reached baseline values within 8 months (93 μmol/L).

Three years after transplantation, during her second pregnancy, albuminuria and acute renal failure (serum creatinine: 149 μmol/L) occurred at 22 weeks of amenorrhea. At 28 weeks of amenorrhea, a hemolytic anemia episode with acute arteriolar TMA lesions led to tacrolimus discontinuation. The patient underwent a caesarian section because of pre-eclampsia, with delivery of a healthy baby.

A month later, serum creatinine was 105 μmol/L with a 3 g/24 hours proteinuria. The graft biopsy performed 6 months later showed glomerular ischemia with 1 FSGS lesion and arteriolosclerosis, but no signs of TMA. A new desire for pregnancy led to azathioprine reintroduction together with low-dose tacrolimus, considering her previous rejection episode.

At 5 years after transplantation and 3 years after the last treatment modification, the patient had a 3-day self-limited viral rhinosinusitis episode. Three weeks later, she was admitted for an oliguric acute renal failure associated with microhematuria and nephrotic range proteinuria. Her complement profile was normal but haptoglobin was low at 102 mg/L (normal range, 412-1693 mg/L). Graft biopsy in light (LM) (Figure 1A-C) and EM showed: acute proliferative endocapillary glomerulonephritis with capillary lumen occlusion caused by neutrophil infiltration and endothelial cell edema, tuft necrosis with karyorrhexis, fibrin and capillary wall rupture, and diffuse and segmental C3 and C1q deposits (C3 > C1q) within glomerular capillary walls. Arteriolar...
lesions with acute and chronic TMA lesions, calcineurin inhibitor-associated arteriolopathy, severe acute ischemic tubular lesions, and advanced interstitial inflammatory fibrosis were also observed. Staining for C4d was negative. No “humps” were found on EM. A PIGN was diagnosed. Renal function slightly improved after methylprednisolone pulses allowing dialysis withdrawal. She was readmitted 1 week later for anuria, and a new graft biopsy showed diffuse acute and chronic arteriolar and glomerular TMA lesions on light microscopy (Figure 1D) and EM (not shown). Most of the glomeruli were ischemic; 2 showed intracapillary fibrin thrombi with neutrophils and another one mesangioclesion with mesangiolysis and 2 FSGS lesions. Glomerular C3 deposition was found by immunofluorescence after incubation with immunoglobulin (Ig)G, IgM, IgA, C1q, C3, C4, C5-9, fibrin, and C4d with no arteriolar deposits to be found. After a single plasma exchange session, 1200 mg eculizumab was given followed by 900 mg weekly for 1 month. No renal function improvement was observed, and the patient remained on chronic dialysis.

A new genetic workup did not show mutation in the coagulation pathway, or any other mutation involving the CHI, CFI, and C3 genes, but identified a homozygous “at-risk” haplotype polymorphism for CHF. This haplotype is made of 5 single nucleotide polymorphisms (rs3753394, -331 C > T; rs800292 (c.184G > A; p.Val62Le); rs1061170 (c.1204 T > C; p.Tyr402His); rs3753396 (c.2016A > G; p.Gln672Gln) and rs1065489 (c.2808G > T; p.Glu936Asp) on the CHF gene and is more prevalent in aHUS cohorts when compared to a control population. We were unable to demonstrate the presence of microchimerism by immunohematology techniques.

As her mother did not harbor mutations involving the MCP, CHF, CFI, or C3 genes, our patient underwent a living-related donor kidney transplantation 7 months after her first graft loss. Prophylactic eculizumab was given from the day of transplantation.

**DISCUSSION**

The CFH haplotype was first described in 2003. It has been associated with aHUS, independently from the presence of other complement-regulation gene mutations, and this association has been confirmed by several authors in independent cohorts. The CFH “at risk” haplotype is also associated with an increased disease penetrance among combined mutation carriers. The risk of recurrence after kidney transplantation is higher in the case of a mutation involving MCP and a mutation in another complement regulation gene when compared to patients with isolated MCP mutation. However, none of the cases reported carried an MCP mutation only combined with the at risk CFH polymorphism.

In our case, 3 TMA episodes were diagnosed after renal transplant. One episode occurred after a miscarriage, another after a preeclampsia, and the last episode after a viral infection. Because we did not have knowledge of the CFH “at risk” haplotype, the first 2 posttransplant TMA recurrences were attributed to other causes (miscarriage followed by T cell-mediated rejection, preeclampsia) triggered by calcineurin-inhibitor toxicity. In the last episode that led to dialysis, an “atypical” PIGN followed by TMA were found in the serial graft biopsies at 5 years after transplantation. A posteriori, the clinical course of our patient favors a C3GN diagnosis. The association of aHUS/TMA and glomerulopathies remains rare. In a retrospective analysis of 248 biopsy-proven glomerulopathies, 6 patients developed aHUS 1 to 36 months after their initial diagnosis of primary FSGS (n = 1), type 1 MPGN (n = 2), C3GN (n = 1), granulomatosis with polyangiitis (n = 1), and Schönlein-Henoch purpura (n = 1). Interestingly, 5 of these 6 patients carried the CFH “at risk” haplotype. This shift between C3GN and TMA has been described in kidney transplant recipients. A woman with antifactor H antibodies developed MPGN on native kidneys, rapid recurrent MPGN on her first kidney graft, and then TMA on her second kidney graft. Atypical hemolytic uremic syndrome recurrence has been reported with isolated MCP in 5 kidney transplant recipients (including our patient). Among them, 3 patients carried the “at-risk” CFH haplotype, including our case. As previously highlighted, aHUS needs prompt treatment with the specific anti-C5 monoclonal antibody, eculizumab, to achieve a favorable outcome. Our patient received eculizumab 21 days after initial presentation, which was probably too late to reverse the activation of the complement.

This case highlights a possible role for the “at risk” CFH haplotype in the development of various complement-associated disorders renal phenotypes. Further studies are needed before assuming that these phenotypes occur as a continuum of the same disease. Another key message is that in an aHUS patient at low recurrence risk after kidney transplantation, TMA should prompt a new genetic workup for any newly discovered mutations or “at risk” haplotypes before considering alternative diagnosis. Eculizumab should also be considered.

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