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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 glomerulonephritis 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.

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Atypical hemolytic uremic syndrome (aHUS) typically associates a hemolytic anemia, a thrombocytopenia, and a renal thrombotic microangiopathy (TMA) potentially leading to end-stage renal disease (ESRD) and associated with a high incidence of mortality. Half of aHUS patients have a demonstrated mutation in genes coding for complement regulation proteins.[1,2] *MCP* codes for the transmembrane cofactor glycoprotein (MCP). It is largely expressed at the surface of renal endothelial cells.[2] An *MCP* mutation leads to complement dysregulation in familial and sporadic aHUS cases.[2]

Glomerulonephritis associated with complement disorders have been reclassified.[3] C3 glomerulopathy, involving an activation of the alternative pathway of complement, includes C3 glomerulonephritis (C3GN) and dense deposit disease. Postinfection glomerulonephritis (PIGN) on the other hand, involves both classic and alternative pathways. It is defined as a nephritic syndrome occurring 1 to 3 weeks after a bacterial infection[4] usually associated with spontaneous remission.[5] In a 2013 clinicopathological study evaluating 11 diagnosed "atypical PIGN" (not self-resolving or leading to end-stage renal disease) cases, all patients harbored complement alternative pathway abnormalities[6] and histopathology findings showed proliferative glomerulonephritis with bright C3 immunofluorescence staining and "humps" on electron microscopy (EM).[5,6]

Genetic workup has improved aHUS recurrence risk stratification after renal transplantation.[7,8] Isolated *MCP* mutation is at low risk of recurrence after kidney transplantation, and only 4 cases have been reported so far.[9,10] Here, we describe a case of C3GN followed by TMA after kidney transplantation, in a patient carrying

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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

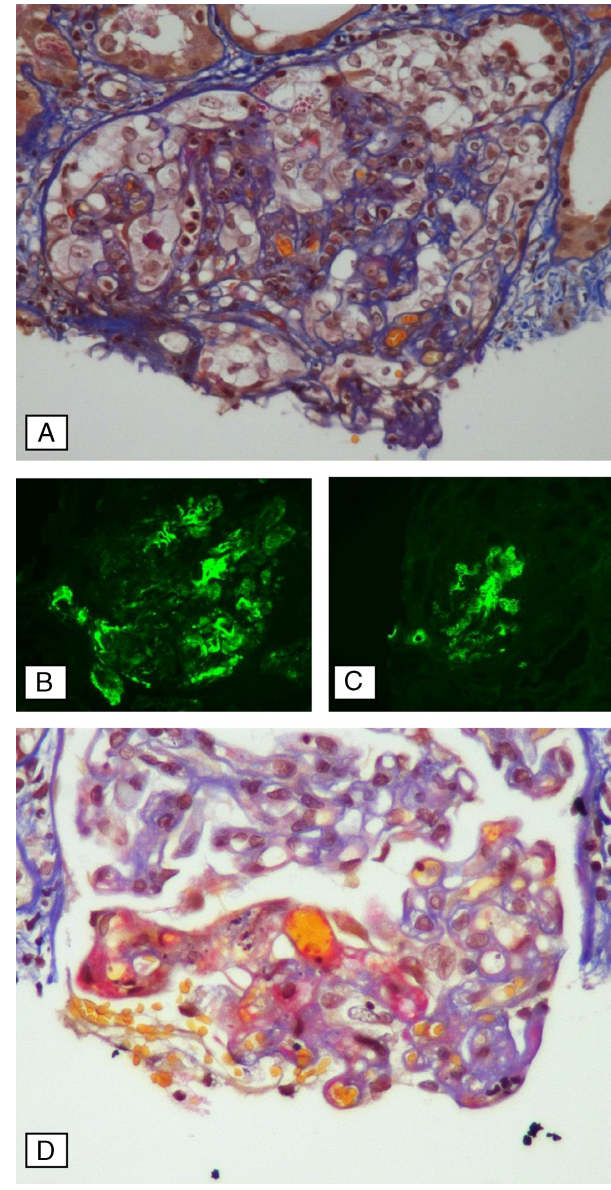

FIGURE 1. Histopathological findings at 5 years after transplantation. Acute proliferative endocapillary glomerulonephritis with capillary lumen occlusion caused by neutrophil infiltration and endothelial cell edema. Tuft necrosis with karyorrhexis, fibrin thrombi, and capillary wall rupture. Acute and chronic TMA and calcineurin inhibitor-associated arteriolopathy with severe acute ischemic tubular lesions and advanced interstitial inflammatory fibrosis (A) (Masson trichrome stain), and, by immunofluorescence, diffuse and segmental C3 (B) and C1q (C) deposits within glomerular capillary walls. Staining for C4d was negative by immunofluorescence using anti-g antibody (not shown). A second biopsy followed 2 weeks later. Diffuse acute and chronic arteriolar and glomerular TMA lesions on light microscopy (D) (Masson trichrome stain) with glomerular C3 depositions (not shown). Original magnification: 400× for (A) and (D) and 300× for (B) and (C).

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 mesangiosclerosis 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,[11] or any other mutation involving the *CFH, CFI,* and *C3* genes, but identified a homozygous "at-risk" haplotype polymorphism for *CFH*. This haplotype is made of 5 single nucleotide polymorphisms (rs3753394, -331 C > T; rs800292 (c.184G > A; p.Val62Ile); rs1061170 (c.1204 T > C; p.Tyr402His); rs3753396 (c.2016A > G; p.Gln672Gln) and rs1065489 (c.2808G > T; p.Glu936Asp) on the *CFH* gene and is more prevalent in aHUS cohorts when compared to a control population.[12] We were unable to demonstrate the presence of microchimerism by immunochemistry techniques.

As her mother did not harbor mutations involving the *MCP*, *CFH*, *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.[13] 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.[12,14] The *CFH* "at risk" haplotype is also associated with an increased disease penetrance among combined mutation carriers.[8] 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.[8] 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.[15] 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.[16] Atypical hemolytic uremic syndrome recurrence has been reported with isolated *MCP* mutation in 5 kidney transplant recipients (including our patient). Among them, 3 patients carried the "at-risk" *CFH* haplotype, including our case.[7,10] As previously highlighted,[17] 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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