Monoclonal Gammopathy of Renal Significance Causes C3 Glomerulonephritis Via Monoclonal IgG Kappa Inhibition of Complement Factor H

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Monoclonal gammopathy of renal significance (MGRS) describes a causal relationship between abnormal circulating monoclonal immunoglobulins (MIg) and kidney disease in the absence of multiple myeloma.[1,S1,S2] Treatment targeting MIg has improved outcomes.[1,S1] Kidney disease associated with MGRS commonly recurs after kidney transplantation if not adequately treated; therefore, an accurate pre-transplantation diagnosis is essential to guide therapy and mitigate recurrence risk.[2,S3]

A high-risk subset of MGRS with dominant glomerular C3 glomerulopathy (C3G) has been reported.[3,S4]

In MGRS-C3G, abnormal paraproteins are not deposited in the kidney; rather, injury occurs via dysregulation of the alternative complement pathway.[3,S4] The resulting acute kidney injury or recurrence is often rapid and severe, with poor prognosis.[4–5,S5]

We report a patient and the specific mechanism for MGRS-C3G that resulted in end-stage renal disease due to immunoglobulin G (IgG) kappa light chain anti–factor H antibodies. Once an accurate diagnosis was made, appropriate treatment of the acquired mechanism enabled successful kidney transplantation. This case shows the importance of accurate diagnosis and appropriate treatment of MGRS.

CASE REPORT

In 2010, a 64-year-old man presented with dyspnea, elevated serum creatinine (4.6 mg/dl), hematuria (3+), proteinuria (3.7 g/24 h). Serum C3 was low, C4 normal, and antinuclear antibody negative (Table 1). Serum (1 g/dl) and urine monoclonal IgG kappa band were identified. Serum free light chains revealed elevated kappa (3.3 mg/dl) and lambda (2.2 mg/dl) levels, with a normal ratio (1.5). Further investigation included normal serum immunoglobulin levels, elevated β2-microglobulin (6390 μg/l), and negative positron emission tomography/computed tomography. Bone marrow biopsy revealed a hypercellular marrow with 5% to 10% plasma cells and 1% population of abnormal kappa light chain–restricted plasma cells by flow cytometry. Kidney biopsy showed a membranoproliferative injury pattern with minimal mesangial hypercellularity and rare subepithelial "hump-like" deposits (Figure 1). Immunofluorescence was positive for C3 in a granular mesangial distribution, but negative for immunoglobulin deposition, including kappa or lambda light chains. The patient was diagnosed with membranoproliferative glomerulonephritis, type 1 – immune complex glomerulonephritis.

Given the absence of direct end-organ damage, M-spike (1.1 g/dl) and normal kappa/lambda ratio, he was diagnosed with monoclonal gammopathy of undetermined significance. He progressed to end-stage renal disease, initiated hemodialysis, and was approved for kidney transplantation.

The patient was called for a potential kidney transplant in 2014, and the kidney biopsy was re-evaluated in light of greater knowledge of complement-mediated glomerular diseases. The biopsy was reinterpreted as

Table 1. Biomarker results

Assay (reference range)	Initial test	+4 Months	+12 Months post bortezomib	+19 Months post bortezomib	+24 Months pre-transplantation	+27 Months post-transplantation
CH50 (30-90 U/ml)	ND	*17*	*47*	54	57	72
AP functional assay (50% to 130%)	*0.1**	*0.2*	99	101	96	95
Hemolytic assay (<0.3%)	0	0	0	0	0	0
FH autoantibody (<1:50+)	*1:400+*	*1:200+*	<1:50+	<1:50+	<1:50+	<1:50+
FB autoantibody	Neg	Neg	Neg	Neg	Neg	Neg
IFE (<7.5%)	*23.3*	*25.4*	2.9	5	4.7	6.1
C3Nef	Neg	Neg	Neg	Neg	Neg	Neg
C4Nef	Neg	Neg	Neg	Neg	Neg	Neg
C3 (0.9-1.8 g/l)	*0.4*	*0.4*	1.6	1.7	1.5	1.5
C4 (0.15-0.57 g/l)	0.28	ND	ND	0.4	ND	ND
C3d (<0.7 mg/l)	ND	0.86	*0.1*	ND	ND	ND
C3c (<1.5mg/l)	ND	ND	*0.58*	*1.2*	*1.4*	*0.9*
FB (22-50 mg/dl)	*13.7*	*20.8*	29.9	35.4	31.7	30.4
Ba (<1.2 mg/l)	ND	*12.5*	*3.5*	*3.5*	*3.1*	1.3
Bb (<2.2 mg/l)	*3.3*	*5.6*	0.6	1.2	1.1	0.8
C5 (10-21 mg/dl)	16.3	18.9	21.5	21.3	18.1	18.2
Properdin (10-33 mg/l)	*9.0*	13.9	15.8	16.4	18.8	16.6
sC5b-9 (<0.3 mg/l)	*0.48*	*0.37*	0.2	0.22	0.21	0.29
FH (45-80 mg/l)	ND	71	63	70	ND	72
FI (16-40 mg/l)	ND	ND	ND	ND	ND	34.6

AP, alternate pathway; C3Nef, C3 nephritic factor; C4Nef, C4 nephritic factor; CH50, complement hemolytic activity 50%; FB, factor B; FH, factor H; FI, factor I; Ba, factor Ba; Bb, factor Bb; Neg, negative; ND, not done;
*Abnormal results in italics.

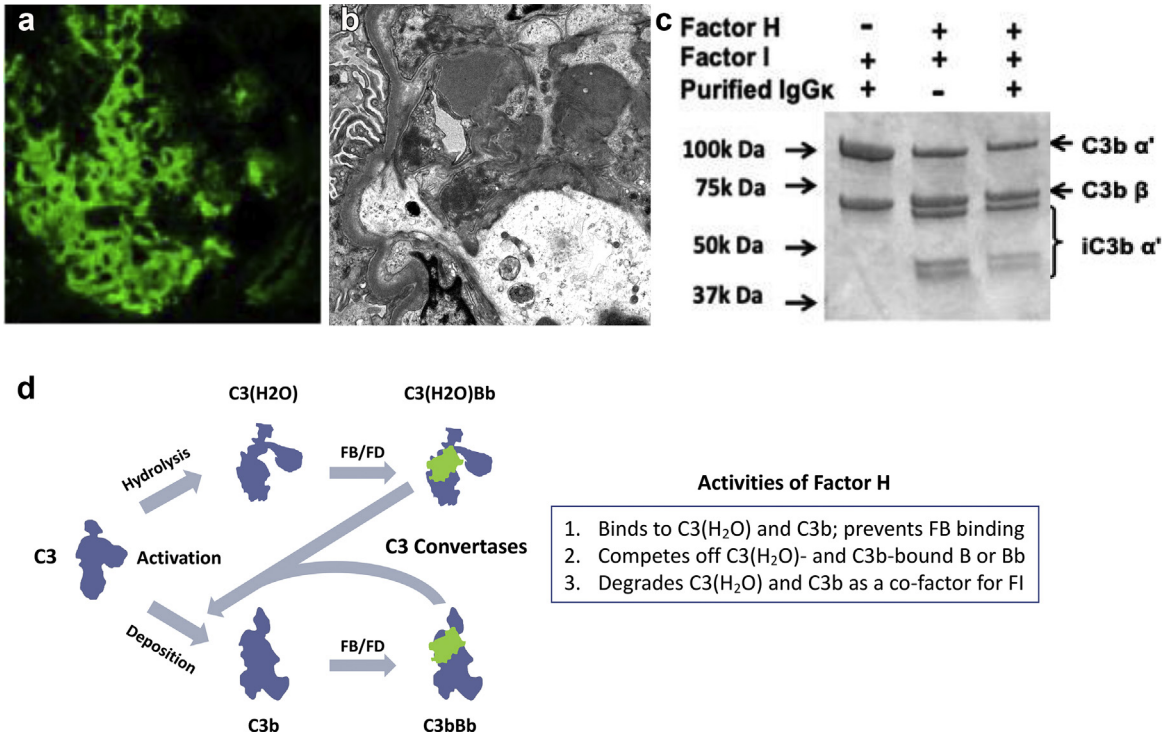

Figure 1. Kidney biopsy. (a) Immunoflourescence image reveals granular mesangial C3 staining. (b) Electron mocroscopy (EM) image reveals scattered mesangial and rare subepithelial "hump-like" deposits without a specific substructure. (c) Cofactor assay. Functional assay of factor H cofactor activity using purified C3b incubated with factor H, factor I and increasing amounts of purified patient immunoglobulin G (IgG) kappa (κ) proteins at 37°C for 20 minutes. The amount of C3b breakdown products (α'68, α'46, and α'43) decrease in the presence of IgG κ suggesting that IgG κ blocks factor H cofactor activity. (d) Activities of factor H. C3 is spontaneously hydrolyzed to C3(H_2O) at a slow but constant rate. More C3 convertase [C3(H_2O)Bb] can be generated when the functions of regulatory proteins, such as factor H (list in the boxes), are compromised. Deposition of tissue-bound C3b and C3 convertase (C3bBb) will then follow.

C3 GN and the transplantation was canceled due to high risk of C3 GN recurrence while his complement dysregulation was further investigated.

He was found to have two normal copies of complement factor H (*CFH)* and complement factor H related protein (*CFHR)* genes (*CFHR1* through *CFHR5*) and no causative variant in complement genes of the AP (*C3*, *CFB*, *CFH*, *CFI,* and *CD46*) using a targeted sequencing panel.[S6] Complement studies identified anti–factor H antibody (1:400+) without C3 nephritic factors. Biomarker study revealed decreased C3 and factor B and elevated soluble C5b-9 level. Modified immunofixation electrophoresis (1:1 mixing of patient and normal sera followed by gel electrophoresis and incubation with anti-C3 antibodies) detected C3 breakdown products consistent with patient-derived IgG kappa directly increasing alternate pathway (AP) activity. Subsequent studies showed that his monoclonal IgG kappa directly bound to the N terminus of factor H (first four short consensus repeat domains), functioning as a blocking autoantibody and impairing factor H cofactor regulatory activity with factor I (cofactor assay) (Figure 1c and 1d).

Based on the causative role of the monoclonal IgG kappa and with the goal to prevent systemic and recurrent C3G after transplantation, he received targeted therapy with cyclophosphamide 300 mg/m^2 orally weekly, bortezomib 1.5 mg/m^2 weekly, and dexamethasone 40 mg orally weekly for eight 28-day cycles. This treatment resulted in disappearance of IgG kappa and anti–factor H antibody and normalization of complement levels and functional assays (Table 1, Figure 1). Maintenance bortezomib 1.3 mg/m^2 every 3 weeks was continued until he received a kidney transplant 1 year later with antithymocyte globulin (200 mg total) and methylprednisolone induction, followed by tacrolimus, mycophenolic acid, and prednisone maintenance immunosuppression.

The kappa/lambda ratio (18.31) increased at 2 months after transplantation but normalized (1.07) after 1 month of weekly bortezomib 1.3 mg/m^2, followed by every 3-week injections for the next 2 years. Post-transplantation serum creatinine nadir was 1.68 mg/dl, with 0.3 g/g proteinuria. A kidney transplant biopsy specimen revealed acute tubular injury without acute rejection, C3 GN, or immune complex injury. Four years post-transplantation, while he receives tacrolimus, mycophenolic acid, and prednisone, his kidney function remains stable (creatinine 1.7-2.0 mg/dl) with minimal proteinuria (0.3 g/g), resolution of nondysmorphic red blood cells on urine microscopy, normal C3 and complement factor H (CFH), undetectable IgG kappa, and no donor-specific antibodies.

DISCUSSION

MGRS is defined as kidney disease caused by an MIg produced by a nonmalignant B cell clone in patients who do not meet the diagnostic criteria for multiple myeloma or other B-cell malignancies. The spectrum of kidney diseases reflects direct and indirect injury.

An example of indirect injury is MGRS leading to C3G, caused by dysregulated AP activity, complement deposition, and related inflammation. C3G is subclassified as dense deposit disease (DDD) or C3 GN based on the electron microscopy pattern of electron-dense deposits. The dysregulation is facilitated by genetic variants in complement genes or acquired autoantibodies to different complement proteins, including antibodies to C3bBb, the C3 convertase of the AP, and CFH, the primary regulator of complement activity. In this case, the presence of a clonal factor H autoantibody hampers factor H cofactor activity with factor I and the efficiency of C3b degradation is compromised. As a consequence, AP activity is increased in the fluid phase as indicated by the high immunofixation electrophoresis.

CFH is a critical complement regulator of the alternative pathway in blood and on cell surfaces (Figure 1d). Inadequate recognition of host cell surfaces by factor H due to mutations and polymorphisms have been associated with complement-mediated tissue damage and disease. CFH blocks the binding of complement factor B and its activated form Bb to C3b, thereby prohibiting production of C3 convertase that cleaves C3 to produce more C3b. CFH also acts as a cofactor of protease factor I that cleaves C3b into the inert fragments C3d and C3c.

There is evidence that MIg may inhibit regulation of the AP of complement by acting as C3 nephritic factor or by interfering with the function of complement regulatory proteins such as factor H. The MGRS-IgG kappa free light chains can act as mini autoantibodies against the N terminus of CFH, impairing cofactor activity.

The association between monoclonal gammopathy and C3G has been elucidated over time, and an MIg is now identified in 33% to 71% of C3G subjects.[6-7,S7-S10] A recent case series identified a monoclonal gammopathy in 36 of 95 (38%) patients with C3G, and 28 of 43 (65%) patients 50 years and older had an identified MIg.[8,S11-12]

Through an algorithmic assessment of kidney dysfunction involving paraprotein and complement analysis before and after successful plasma cell-directed therapy, we have proven that our patient experienced C3G and end-stage renal disease from monoclonal IgG kappa that directly inhibited CFH regulation of the AP (Table 1, Figures 1 and 2).[S13] Using a bortezomib-based treatment regimen, our patient experienced a dramatic

Figure 2. Teaching points. Algorithm for evaluation of possible monoclonal gammopathy of renal significance (MGRS) or C3 glomerulopathy. ACP, alternative complement pathway; AKI, acute kidney injury, anti-FB, anti–factor B antibodies; anti-FH, anti–factor H antibodies; CFB, complement factor B; CFH, complement factor H; CFHR5, complement factor H–related protein 5; CFI, complement factor I; CH50, complement hemolytic activity 50%; CKD, chronic kidney disease; DDD, dense deposit disease; DGKE, diacylglycerol kinase E; GN, glomerulonephritis; IFE, immunofixation electrophoresis; MCP, membrane cofactor protein; MPGN, membranoproliferative glomerulonephritis; SFLC, serum free light chains; SPEP, serum protein electrophoresis; UA, urine analysis; UPEP, urine protein electrophoresis.

improvement in pretransplantation serologic markers, abrogation of anti–factor H activity, normalization of complement levels, and excellent post-transplantation kidney function despite an early transient relapse.

A recent case series of kidney transplant recipients with primary C3G experienced recurrence (10 of 12 patients) in a median time of 14 months and graft failure in 42 months.[4] Given a C3G recurrence risk of 35% to 65% in kidney transplant recipients, each patient requires careful evaluation before transplantation.[3]

Optimal C3G treatment when associated with an MIg remains unclear. Patients have been treated with a range of immunosuppressive therapies including prednisone, azathioprine, mycophenolate, calcineurin inhibitors, and cyclophosphamide with mixed results. Therapy has directly targeted cells producing the monoclonal protein with anti-CD20 antibody (e.g., rituximab) or proteasome inhibitors (e.g., bortezomib).[6-7] The role of eculizumab remains unclear, with several case reports of salvage therapy showing varying degrees of success.[9]

We advise that the presence of measurable complement dysregulation, regardless of kidney function, requires targeted treatment to achieve disease control and reduce the risk of post-transplantation recurrence. The decision whether to continue treatment post-transplantation should be made by the multidisciplinary clinical team.

CONCLUSION

Comprehensive analysis of unexplained kidney disease is required in the setting of circulating paraproteins. Establishing the precise role of a MIg is important in the diagnosis and treatment of patients with MGRS and should include hematologic and complement pathway analysis. Monoclonal IgG or free light chains cause a significant proportion of C3G with a high risk of post-transplantation recurrence. Treatment with targeted therapy can halt MGRS-C3G disease and enable a successful kidney transplant.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

Consent for this Case Report was obtained from the patient.

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Blosser C, Zhang Y, Dhawale T, Johnson C, Hendrie P, Smith RJH. "C3 Glomerulopathy Secondary To Complement Factor H Inhibition By Monoclonal IgG κ Light Chain." Poster Presentation. American Transplant Congress, Boston, Massachusetts, June 11–16, 2016.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods and Materials

Supplementary References

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